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(54) Title: METHODS FOR TREATING INFLAMMATORY DISEASE BY ADMINISTERING ALDEHYDES AND DERIVATIVES THEREOF

(57) Abstract: A method is disclosed for treating inflammatory disease in an animal in need thereof by administering to the animal a pharmaceutical composition containing an anti-inflammatory effective amount of an organic aldehyde compound or a derivative thereof in a pharmaceutically acceptable vehicle.

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METHODS FOR TREATING INFLAMMATORY DISEASE BY ADMINISTERING ALDEHYDES AND DERIVATIVES THEREOF

Background

Field

[0001] The field relates to organic aldehydes and derivatives thereof, and in particular to methods of administering pharmaceutical compositions containing such compounds to treat inflammatory diseases.

Description of the Related Art

[0002] Many acute and chronic inflammatory diseases are thought to be caused by pathological immune responses. Tissue injury caused by ischemia, reperfusion or physical trauma is aggravated by inflammatory reactions. The natural resolution of inflammation is often incomplete, leading to chronic pathological conditions associated with pain and functional impairment of the affected tissues. Although many drugs in present use reduce pain and inflammatory damage, there is still an urgent need for better treatments for a wide variety of inflammatory diseases.

[0003] Rheumatoid arthritis is a well known example of an inflammatory disease for which improved treatments are needed (Saravanan et al., *Expert Opin. Pharmacother.* 3:845-56 (2002); O'Dell, *N. Engl. J. Med.* **350**:2591-602 (2004)). Typically, rheumatoid arthritis patients are first treated with nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, indomethacin, ibuprofen and many others (Steinmeyer, *J. Arthritis Res.* 2:379-85 (2000)). These drugs inhibit the first step of prostaglandin synthesis by competitively inhibiting the enzymes cyclooxygenase 1 and 2 (COX-1 and COX-2). In general, NSAIDs provide only symptomatic relief from the pain and inflammation associated with the disease, and do not arrest the progression of pathological injury to the joints. Moreover, the use of these drugs is limited by side effects, in particular gastrointestinal ulcers that are thought to be caused by the inhibition of COX-1. More recently developed selective COX-2 inhibitors have fewer gastrointestinal side effects, but increase the risk of myocardial infarction (Ardoin et al., *Curr. Opin. Rheumatol.* 18:221-226 (2006)).

[0004] In contrast to NSAIDs, glucocorticoids are potent suppressors of immune responses and inflammation. However, the continued use of glucocorticoids at supraphysiological doses is associated with many adverse effects, some of which are severe, such as hypertension, increased susceptibility to infections, osteoporosis, growth arrest and behavioural disturbances.

Withdrawal from corticosteroid therapy can lead to disease flare-up and also acute adrenal insufficiency.

[0005] Several other drugs that are able to reduce the progression of rheumatoid arthritis, at least in some patients, are collectively referred to as disease modifying anti-rheumatic drugs (DMARDs). Examples include methotrexate, chloroquine, sulfasalazine, gold salts, D-penicillamine, azathioprine, leflunomide and cyclosporine. DMARDs are now often used earlier in the course of disease (Scott, *Arthritis Res. Ther.* 6:15-8 (2004)). While these drugs may arrest or reduce the progression of joint destruction, they have a variety of adverse effects, some of which may be severe, leading to the withdrawal of the drug from the treatment schedule.

[0006] Recently, a significant improvement in the treatment of rheumatoid arthritis has been achieved with a novel class of DMARDs often referred to as biologics (Olsen et al., *N. Engl. J. Med.* 350:2167-2179 (2004)). Biologics are therapeutically effective proteins that are engineered and expressed using recombinant DNA technologies. Some important biologics currently used for the treatment of rheumatoid arthritis are tumor necrosis factor (TNF) neutralizing antibodies and TNF receptor constructs. These new anti-rheumatic drugs have a quicker onset of action than the traditional DMARDs, and suppress the progression of joint erosions. However, this class of drugs must be parenterally administered and is quite costly. Moreover, extended use of TNF neutralizing biologics has revealed adverse effects, such as reactivation of tuberculosis, increased susceptibility to infections, and an increased risk for development of malignant diseases (Mikuls et al., *Drug Saf.* 26:23-32 (2003)).

[0007] Because of the shortcomings of the existing drugs used for treating rheumatoid arthritis and other inflammatory diseases, extensive efforts are being made by the pharmaceutical and biotechnology industries to develop novel treatment modalities that are safe and effective (Kumar et al., *Nat. Rev. Drug Discov.* 2:717-26 (2003); Adcock, *Drug Discovery Today: Therapeutic Strategies*, 1:321-9 (2004); Smith, *Drug Discovery Today* 10:1598-1606 (2005)). One molecule that has been identified as potentially useful in treating inflammatory disease is carbon monoxide. Carbon monoxide (CO) is an endogenous metabolite with pleiotropic effects that are integrated into adaptive responses of the body to various types of stress (Ryter et al., *Bioessays*, 26: 270-80 (2004)). CO inhibits TNF production *in vitro* and *in vivo*, and has shown impressive anti-inflammatory effects in animal models (Otterbein, *Antioxid. Redox. Signal.* 4:309-319 (2002); Ryter et al., *Bioessary* 26:270-280 (2004)). In addition to inhibiting TNF production, CO has other anti-inflammatory effects. It inhibits the production of other pro-inflammatory cytokines, such as IL-1, IL-6 and MIP-1 (Otterbein et al., *Nat. Med.* 6:422-428

(2000); Morse et al., *J. Biol. Chem.* 278:36993-36998 (2003)), enhances IL-10 production (Otterbein et al., *Nat. Med.* 6:422-428 (2000)), inhibits excessive NO production by inducible nitric oxide synthase (Sarady et al., *Faseb J.* 18:854-856 (2004)), inhibits mast cell activation (Ndisang et al., *Immunopharmacol.* 43:65-73 (1999)), and modulates immune responses (Song et al., *J. Immunol.* 172:1220-1226 (2004)).

[0008] Often, however, endogenous carbon monoxide (CO) does not provide its full potential of beneficial effects, because its production is delayed or reduced under pathological conditions. Thus, therapeutic effects may be achieved by administration of exogenous carbon monoxide. Exogenous CO may also induce the expression of hemoxygenase-1 (HO-1) (Sawle et al., *Br. J. Pharmacol.* 145(6):800-810 (2005); Lee et al., *Nat. Med.* 8:240-246 (2002)). HO-1 is known to have a wide variety of protective functions (Otterbein et al., *Trends Immunol.* 24:449-455 (2003)), most of which are mediated by its products CO and biliverdin/bilirubin. Thus, the beneficial effects of exogenous CO may be further augmented by the induction of endogenous CO and biliverdin/bilirubin production.

[0009] Indeed, treatment of animals by inhalation of carbon monoxide has revealed beneficial effects in a variety of disease models. However, systemic delivery of carbon monoxide via the lung is not practical outside of hospitals, and is limited by the requirement for doses that are near toxic levels. Limitations of carbon monoxide inhalation therapy may be overcome by the use of carbon monoxide releasing molecules, also known as CORMs (Motterlini et al., *Curr. Pharm. Des.* 9:2525-39 (2003)). Impressive therapeutic effects of CO used as a gas and CORMs have been achieved in animal models of inflammation (Sarady et al., *Faseb J.* 18:854-6 (2004); Zuckerbraun et al., *Am. J. Physiol. Gastrointest. Liver Physiol.* 289: G607-13 (2005); Sawle et al., *FEBS Lett.* 508:403-6 (2001)), ischemia/reperfusion injury (Amersi et al., *Hepatology*, 35:815-23(2002); Nakao et al., *Am. J. Pathol.* 163:1587-98 (2003); Zhang et al., *J. Biol. Chem.* 278:1248-58 (2003); Vera et al., *J. Am. Soc. Nephrol.* 16:950-8 (2005); Sandouka et al., *Kidney Int.* 69:239-47 (2006)), postoperative ileus (Moore et al., *Crit. Care Med.* 33:1317-26 (2005)), transplantation (Chauveau et al., *Am. J. Transplant.* 2:581-92 (2002); Clark et al., *Circ. Res.* 93:e2-8 (2003); Gunther et al., *Diabetes* 51:994-9 (2002); Akamatsu et al., *Faseb J.* 18:771-2 (2004); Martins et al., *Transplant. Proc.* 37:379-81(2005)), atherosclerosis (Otterbein et al., *Nat. Med.* 9:183-90 (2003)), restenosis (Otterbein et al., *Nat. Med.* 9:183-90 (2003)), myocardial infarction (Stein et al., *J. Mol. Cell. Cardiol.* 38:127-34 (2005); Guo et al., *Am. J. Physiol. Heart Circ. Physiol.* 286:H1649-53 (2004)) and pulmonary hypertension (Zuckerbraun et al., *J. Exp. Med.* 203:2109-19 (2006)).

[0010] While the potential advantage of CO delivery by CORMs over CO delivery by inhalation is generally recognized, the identification of CORMs which selectively deliver CO to therapeutic targets remains a challenge in the development of CORMs as drugs. Selective delivery of CO to diseased tissues may be achieved by using compounds that release CO in the presence of reactive oxygen species, which are generated at high levels under many pathological conditions. Reactive oxygen species (ROS) include, without limitation, oxygen ions, superoxide, peroxynitrite, free radicals and peroxides, both inorganic and organic. A variety of highly reactive ROS are generated from superoxide (Hogg, *Semin. Reprod. Endocrinol.* 16:241-8 (1998)). These molecules are generated at low levels in many tissues, and have important roles in various signal transduction pathways (Droge, *Physiol. Rev.*, 82:47-95 (2002)). However, excessive production of ROS occurs in many pathological conditions. While a variety of mechanisms have evolved to prevent damage by excessive amounts of ROS, conditions in which production of these highly reactive molecules exceeds the capacity to neutralize them are referred to as oxidative stress. "Oxidative stress" is a medical term for the damage to animal or plant cells caused by reactive oxygen species.

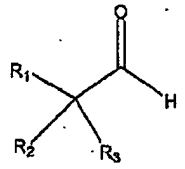
[0011] Oxidative stress is a hallmark of many diseases (Spector, *J. Ocul Pharmacol Ther.* 2:193-201(2000)). These include inflammatory diseases, such as rheumatoid arthritis (Bauerova et al., *Gen. Physiol. Biophys.* 18 Spec No:15-20 (1999); Hadjigogos, *Panminerva Med.* 45:7-13 (2003); Hitchon et al., *Arthritis Res. Ther.* 6:265-78 (2004)), asthma (Andreadis et al., *Free Radic. Biol. Med.* 35:213-25 (2003); Henricks et al., *Pulm. Pharmacol. Ther.* 14:409-20 (2001)), ulcerative colitis (Suzuki et al., *Scand. J. Gastroenterol.* 36:1301-6 (2001)), and diseases associated with chronic inflammatory reactions, such atherosclerosis and neurodegenerative diseases (Beal, *Free Radic. Biol. Med.* 32:797-803 (2002)), and/or with ischemia/reperfusion injury, such as myocardial infarction (Frangogiannis et al., *Cardiovasc. Res.* 53:31-47(2002)), stroke, sleep apnea and transplantation. New CORM compositions that release CO in the presence of reactive oxygen species would be useful for treating inflammatory diseases such as these.

Summary

[0012] Disclosed herein are methods of treating inflammatory disease in an animal by administering a pharmaceutical composition containing an organic aldehyde or its derivative. The aldehydes exhibit anti-inflammatory properties, at least in part by release of carbon monoxide (CO) in normal or inflamed tissues, or both. In some instances, an aldehyde is administered in the form of a derivative, *e.g.*, in a protected form that provides, for example, improved *in vivo* stability, bioavailability, and/or delivery *in vivo*.

[0013] Accordingly, one aspect provides a method for treating inflammatory disease. The method includes administering to an animal in need thereof a pharmaceutical composition including an anti-inflammatory effective amount of an organic aldehyde compound or a derivative thereof in a pharmaceutically acceptable vehicle. The organic aldehyde releases CO in the animal, thereby providing an anti-inflammatory effect.

[0014] In certain embodiments, the organic aldehyde is a compound of formula I:



(I)

wherein R_1, R_2 and R_3 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2 and cyano; or two or more of R_1, R_2 and R_3 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure.

[0015] In some embodiments, R_1, R_2 and R_3 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, and substituted alkenyl. In some such embodiments, the compound of formula I is trimethylacetaldehyde, 2,2-dimethyl-4-pentenal, 4-ethyl-4-formyl-hexanenitrile, 3-hydroxy-2,2-dimethylpropanal, 2-formyl-2-methyl-propylmethanoate or 2-ethyl-2-methyl-propionaldehyde.

[0016] In other embodiments, R_1 and R_2 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, and substituted alkenyl, and R_3 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and substituted alkylaryl. In some such embodiments, the compound of formula I is 2,2-dimethyl-3-(*p*-methylphenyl)propanal or 2-methyl-2-phenylpropionaldehyde.

[0017] In certain embodiments, a derivative of a compound of formula I is employed. In some embodiments, the derivative is an acetal, hemiacetal, aminocarbinol, aminal, imine, enaminone, imidate, amidine, iminium salt, sodium bissulfite adduct, hemimercaptal, dithioacetal, 1,3-dioxepane, 1,3-dioxane, 1,3-dioxalane, 1,3-dioxetane, α-hydroxy-1,3-dioxepane, α-hydroxy-1,3-dioxane, α-hydroxy-1,3-dioxalane, α-keto-1,3-dioxepane, α-keto-1,3-dioxane, α-keto-1,3-dioxalane, α-keto-1,3-dioxetane, macrocyclic ester/imine, macrocyclic ester/hemiacetal, oxazolidine, tetrahydro-1,3-oxazine, oxazolidinone, tetrahydro-oxazinone, 1,3,4-oxadiazine, thiazolidine, tetrahydro-1,3-thiazine, thiazolidinone, tetrahydro-1,3-thiazinone, imidazolidine, hexahydro-1,3-pyrimidine, imidazolidinone, tetrahydro-1,3-pyrimidinone, oxime, hydrazone, carbazone, thiocarbazone, semicarbazone, semithiocarbazone, acyloxyalkyl ester derivative, O-acyloxyalkyl derivative, N-acyloxyalkyl derivative, N-Mannich base derivative or N-hydroxymethyl derivative. In some such embodiments, the derivative is an oxazolidine, thiazolidine, imidazolidinone or oxazolidinone.

[0018] In some embodiments, the compound of formula I is linked to an amino acid or protein. In certain embodiments, the compound of formula I or derivative thereof is administered concomitantly with a second anti-inflammatory agent. In certain embodiments, the compound of formula I or derivative thereof is administered in the form of a pharmaceutically acceptable salt.

[0019] In some embodiments, the pharmaceutical composition is a tablet, dragee, capsule, pill, powder, troche or granule. In other embodiments, the pharmaceutical composition is a suspension, emulsion, solution, syrup or elixir. In still other embodiments, the pharmaceutical composition is formulated for parenteral administration.

[0020] In certain embodiments, the inflammatory disease is arthritis, for example, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis or psoriatic arthritis. In some embodiments, the inflammatory disease is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis or multiple sclerosis. In certain embodiments, the inflammatory disease is an inflammatory lung disease. In some embodiments, the inflammatory disease is an inflammatory bowl disease. In certain embodiments, the inflammatory disease is an

inflammatory skin disease. In some embodiments, the inflammatory disease is atherosclerosis, myocardial infarction, stroke or transplant rejection. In certain embodiments, the inflammatory disease is gram-positive or gram negative shock, sepsis, septic shock, hemorrhagic or anaphylactic shock or systemic inflammatory response syndrome.

Brief Description of the Drawings

[0021] The following drawings are presented for the purpose of illustration only and are not intended to be limiting:

[0022] Figures 1A-D are plots showing the CO release behavior of trimethylacetaldehyde (compound 1) in TBHP and pH 2 solutions, and also the effects of concentrations of trimethylacetaldehyde and TBHP on the CO release.

[0023] Figure 2 is a plot showing the kinetics of CO release of 2,2-dimethyl-4-pentenal (compound 2) in TBHP, pH 2 and rpmi solutions.

[0024] Figure 3 is a plot showing the kinetics of CO release of 4-ethyl-4-formyl-hexanenitrile (compound 3) in TBHP, pH 2 and rpmi solutions.

[0025] Figure 4 is a plot showing the kinetics of CO release of 3-hydroxy-2,2-dimethylpropanal (compound 4) in TBHP solution.

[0026] Figure 5 is a plot showing the kinetics of CO release of 2-formyl-2-methyl-propylmethanoate (compound 5) in TBHP solution.

[0027] Figure 6 is a plot showing the kinetics of CO release of 2,2-dimethyl-3-(*p*-methylphenyl)propanal (compound 6) in TBHP, H_2O_2, pH 2 and rpmi solutions.

[0028] Figure 7 is a plot showing the kinetics of CO release of 2-methyl-2-phenylpropionaldehyde (compound 7) in TBHP, H_2O_2 and pH 2 solutions.

[0029] Figure 8 is an overview plot showing the kinetics of CO release for compounds 1-7 in the first 6 hours in TBHP solutions.

[0030] Figure 9 presents an overview of the data on the kinetics of CO release for compounds 1-7 after 24 hours in different media.

[0031] Figure 10 is a plot showing the changes in body weight in untreated (control) and treated (compound 1 or compound 2) Sprague Dawley rats after the induction of adjuvant arthritis.

[0032] Figures 11A-D are plots showing the changes in the volume of the right paw (11A) and the left paw (11B), and of the circumference of the right paw (11C) and the left paw (11D) in untreated (control) and treated (compound 1 or compound 2) Sprague Dawley rats after the

induction of adjuvant arthritis.

[0033] Figure 12 is a plot showing changes in the arthritic index in untreated (control) and treated (compound 1 or compound 2) Sprague Dawley rats after the induction of adjuvant arthritis.

[0034] Figure 13 is a plot showing changes of body weight in untreated and treated Lewis rats after induction of adjuvant arthritis. The treatment groups included compound 1 (100 mg/kg), compound 1 (25 mg/kg), compound 7 (100 mg/kg), compound 7 (25 mg/kg), dexamethasone, and vehicle (carboxymethylcellulose/Tween 80).

[0035] Figure 14 is a plot showing changes in paw volume in untreated and treated Lewis rats after the induction of adjuvant arthritis. The treatment groups included compound 1 (100 mg/kg), compound 1 (25 mg/kg), compound 7 (100 mg/kg), compound 7 (25 mg/kg), dexamethasone, and vehicle (carboxymethylcellulose/Tween 80).

[0036] Figure 15 is a plot showing changes in arthritic index in untreated and treated Lewis rats after the induction of adjuvant arthritis. The treatment groups included compound 1 (100 mg/kg), compound 1 (25 mg/kg), compound 7 (100 mg/kg), compound 7 (25 mg/kg), dexamethasone, and vehicle (carboxymethylcellulose/Tween 80).

[0037] Figure 16 is a plot showing the kinetics of CO release of 2-*tert*-butyl-thiazolidine-4-carboxylic acid (compound 9) in TBHP plus rpmi solution.

[0038] Figure 17 is a plot showing the kinetics of CO release of 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester (compound 10) in TBHP plus rpmi solution.

[0039] Figure 18 is a plot showing the kinetics of CO release of 2-*tert*-butyl-thiazolidine (compound 11) in TBHP plus rpmi solution.

[0040] Figure 19 is a plot showing the kinetics of CO release of 2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid (compound 12) in TBHP plus rpmi solution.

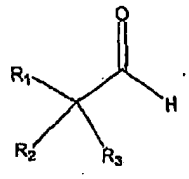
Detailed Description

[0041] All of the patent documents and literature references identified herein are incorporated by reference in their entirety.

[0042] Disclosed herein are methods for treating inflammatory disease in an animal by administering a pharmaceutical composition including an aldehyde compound or a derivative thereof. The therapeutic effects of these compounds are at least in part due to their ability to generate carbon monoxide (CO) under physiological or pathophysiological conditions. In at least some embodiments, CO is generated from the aldehydes or derivatives thereof by

spontaneous release (*i.e.*, release induced by the presence of reactive oxygen species, hydrolysis, pH variation, metabolic activation, or any other biological change that affects the chemical stability of the aldehyde, leading to decarbonylation) in normal or inflamed tissues, or both. In certain embodiments, the aldehydes or derivatives thereof generate CO exclusively or preferentially in the presence of reactive oxygen species (ROS), and thus are expected to have beneficial effects in diseases associated with oxidative stress.

[0043] Compounds for administration as disclosed herein include organic aldehydes of the general formula I:



(I)

wherein R_1, R_2 and R_3 are each independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2 and cyano; or two or more of R_1, R_2 and R_3 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure.

[0044] The following definitions are used herein. "Alkyl" refers to straight or branched chain saturated hydrocarbyl groups having up to 20 carbon atoms, and "substituted alkyl" refers to alkyl groups bearing one or more substituents selected from amino, alkylamino, hydroxy, alkoxy, mercapto, alkylmercapto, aryl, aryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, F, Cl, Br, NO_2, cyano, sulfonyl, sufinyl and similar substituents known to those of skill in the art. "Cycloalkyl" refers to saturated hydrocarbyl groups containing one or more rings and having in the range of 3 to 12 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above. "Heterocyclyl" refers to cyclic groups containing one or more rings including one or more heteroatoms (*e.g.*, N, O or S) as part of the ring structure and having in the range of 3 to 12 ring atoms, and "substituted heterocyclyl" refers to heterocyclyl groups further bearing one or more substituents as set forth

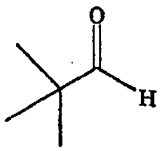
above. "Alkylheterocyclyl" refers to alkyl-substituted heterocyclyl groups, and "substituted alkylheterocyclyl" refers to alkylheterocyclyl groups further bearing one or more substituents as set forth above. "Alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of 2 to 20 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above. "Aryl" refers to aromatic groups having in the range of 6 up to about 14 carbon atoms, and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above. "Heteroaryl" refers to aromatic groups containing one or more heteroatoms (*e.g.*, N, O or S) as part of the ring structure, and having in the range of 5 up to about 13 carbon atoms, and "substituted heteroaryl" refers to heteroaryl groups further bearing one or more substituents as set forth above. "Alkylaryl" refers to alkyl-substituted aryl groups, and "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents as set forth above.

[0045] "Hydroxy" refers to the group OH. "Alkoxy" refers to a group -OR, wherein R is an alkyl group as defined above. "Amino" refers to the group NH_2. "Alkylamino" refers to a group –NHR or -NRR', where R and R' are independently chosen from alkyl or cycloalkyl groups as defined above. "Mercapto" refers to the group SH. "Alkylmercapto" refers to the group S-R, where R represents an alkyl or cycloalkyl group as defined above. "Aryloxy" refers to a group -OAr, wherein Ar is an aryl group as defined above, and "substituted aryloxy" refers to aryloxy groups further bearing one or more substituents as set forth above. "Heteroaryloxy" refers to a group -OHt, wherein Ht is a heteroaryl group as defined above, and "substituted heteroaryloxy" refers to heteroaryloxy groups further bearing one or more substituents as set forth above. "Alkoxycarbonyl" refers to a group –C(O)-OR, wherein R is an alkyl group as defined above.

[0046] "Acyl" refers to a group –C(O)-R, where R is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, as defined above. "Acyloxy" refers to a group –O-C(O)-R, where R is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, as defined above. "Acylamino" refers to a group –NR'C(O)R, where R and R' are each independently chosen from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, as defined above. "Alkylsulfonyl" refers to a group –$S(O)_2R$, where R represents an alkyl or cycloalkyl group as defined above. "Alkylsulfinyl" refers to a group –S(O)R, where R represents an alkyl or cycloalkyl group as defined above.

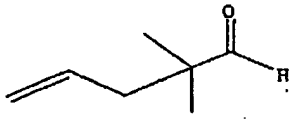
[0047] Non-limiting examples of aldehydes of the general formula I include the following:

trimethylacetaldehyde (compound 1)



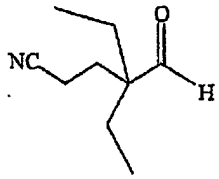
(1);

2,2-dimethyl-4-pentenal (compound 2)



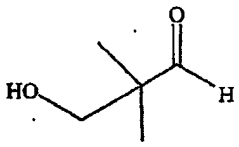
(2);

4-ethyl-4-formyl-hexanenitrile (compound 3)



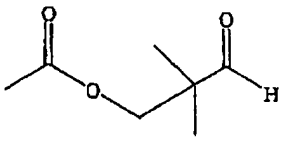
(3);

3-hydroxy-2,2-dimethylpropanal (compound 4)



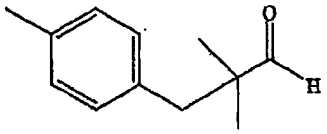
(4);

2-formyl-2-methyl-propylmethanoate (compound 5)



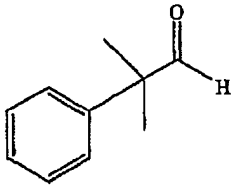
(5);

2,2-dimethyl-3-(*p*-methylphenyl)propanal (compound 6)



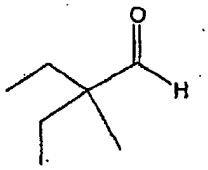
(6);

2-methyl-2-phenylpropionaldehyde (compound 7)



(7);

and 2-ethyl-2-methyl-propionaldehyde (compound 8)



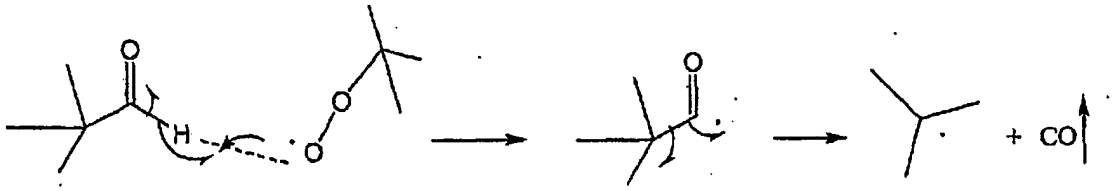
(8).

[0048] The most common reactions known for the decarbonylation of aldehydes require drastic conditions, such as strong acidic or basic conditions, high temperatures together with ultraviolet light, radical initiators and/or the presence of a metal catalyst (Jerry March, *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, John Wiley & Sons, 4th Ed., 1992). However, highly branched aldehydes have been observed to decarbonylate at room temperature when irradiated by ultraviolet light (Berman et al., *J. Am. Chem. Soc.*, 85:4010-4013 (1963); Conant et al., *J. Am. Chem. Soc.* 51:1246-1255 (1929)). The loss of carbon monoxide from tertiary aldehydes leads to tertiary radicals, which are more stable than primary or secondary radicals due to resonance stabilization by hyperconjugation. Hyperconjugation includes the stabilization that results from the interaction of electrons in a σ-bond (usually C-H or C-C) with an adjacent empty (or partially filled) p-orbital or π-orbital to give an extended molecular orbital that increases the stability of the system. Thus, decarbonylation is favored in tertiary aldehydes, as compared to primary and secondary aldehydes.

[0049] The inventors have found that the tertiary aldehydes disclosed herein advantageously release CO in the presence of certain reactive oxygen species at room temperature, and thus are expected to be capable of targeting and releasing therapeutic CO into inflamed tissues. In

addition, many of the tertiary aldehydes disclosed herein do not release CO in water, which is also expected to be useful for purposes of targeting inflamed tissue. Furthermore, tertiary aldehydes such as those disclosed herein are expected to have potentially fewer side effects than primary or secondary aldehydes. This is because tertiary aldehydes, having a higher branching and a less electrophilic carbonyl group, are less reactive towards nucleophiles, and therefore less prone to interact with nucleophilic biomolecules (E. Schauenstein, H. Eserbauer & H. Zollner, *Aldehydes in Biological Systems, Their Natural Occurrence and Biological Activity*, Pion Limited, 1977, Ch. 1-2). Indeed, tertiary aldehydes reportedly are less likely than primary and secondary aldehydes to interfere with DNA or inactivate cytochrome P450 (Adam et al., *Free Radical Biol. Med.*, 26:566-79 (1999); Raner et al., *Biochem.* 36:4895-4902 (1997)).

[0050] While not to be bound by any particular theory, the following equation 1 shows a proposed mechanism for the decarbonylation of tertiary aldehydes (exemplified by trimethylacetaldehyde (compound 1)) by reactive oxygen species, generating carbon monoxide and a stabilized tertiary radical:



(1)

[0051] Accordingly, in certain embodiments, the aldehyde is a tertiary aldehyde. In such embodiments, the aldehyde is a compound of the above formula I in which R_1, R_2 and R_3 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2 and cyano; or two or more of R_1, R_2 and R_3 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure.

[0052] In some embodiments, the aldehyde is an optionally substituted alkyl or alkenyl tertiary aldehyde. In particular, the aldehyde is a compound of formula I in which R_1, R_2 and R_3 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, and substituted alkenyl. Non-limiting examples include the above-identified compound 1 (simple alkyl), compound 2 (simple alkenyl), compound 3 (cyano-substituted alkyl),

compound 4 (hydroxyl-substituted alkyl), compound 5 (acyloxy-substituted alkyl) and compound 8 (simple alkyl).

[0053] In some embodiments, the aldehyde is an alkyl or alkenyl tertiary aldehyde with one aromatic or alkylaromatic substituent. Specifically, the aldehyde is a compound of formula I in which R_1 and R_2 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, and substituted alkenyl, and R_3 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and substituted alkylaryl. Non-limiting examples include the above-identified compound 6 (alkylaryl), and compound 7 (aryl).

[0054] In some embodiments, the aldehyde is a trialkyl or triaryl substituted aldehyde. Specifically, the aldehyde is a compound of formula I in which R_1, R_2 and R_3 are alkyl, or in which R_1, R_2 and R_3 are aryl.

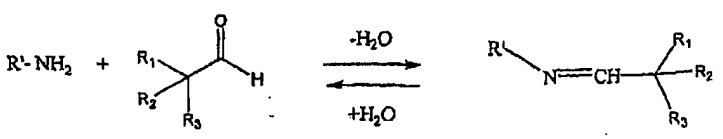
[0055] In some instances, for example, to improve the *in vivo* stability, bioavailability, or pharmacokinetic properties of a therapeutic aldehyde, the aldehyde is administered in the form of a derivative, or a protected form thereof. The derivative serves as a source of the free or unmodified aldehyde *in vivo* and/or releases CO *in vivo* itself. In certain embodiments, an aldehyde derivative is generated that acts as a prodrug, a pharmacologically inactive chemical entity that, when chemically transformed or metabolised in an animal, is converted into a pharmacologically active substance. The generation of the therapeutically effective molecule (*i.e.*, the aldehyde) from the prodrug occurs prior to, during or after reaching the site of action within the body (Bundgaard et al., *Int. J. Pharm.* 13:89-98 (1983)). Release of the aldehyde from the prodrug generally occurs via chemical or enzymatic lability, or both, within the body system.

[0056] Examples of aldehyde prodrugs that are chemically labile include, without limitation, non-cyclic chain compounds that exist in equilibrium in physiological media, such as Mannich base derivatives, imines, oximes, amidines, hydrazones and semicarbazones (WO 2006/012215; Herrmann et al., *Chem. Commun.* 2965-2967 (2006); Deaton et al., *Bioorg. Med. Chem. Lett.* 16:978-983 (2006)), and ring chain tautomeric prodrugs such as 1,3-X,N-heterocycles (X = O, S, NR) (Valters et al., *Adv. Heterocycl. Chem* 64:251-321 (1995); Valters et al., *Adv. Heterocycl. Chem.* 66:1-71 (1996)) that are prepared from the reaction of difunctional compounds with aldehydes. From the ring chain equilibria of these derivatives, the open form undergoes hydrolysis to give the bioactive molecule. In both cases, the ratios of the species involved in the equilibria of these systems are strongly influenced by the steric and electronic characters of the substituents.

[0057] An alternative strategy is to generate prodrugs that are converted to the pharmacologically active compound by an enzymatic process (Bernard Testa & Joachim M. Mayer, *Hydrolysis in Drug and Prodrug Metabolism, Chemistry, Biochemistry and Enzymology* WILEY-VCH, 2003). There are several types of chemical groups such as, for example, esters, amides, sulphates and phosphates, that are readily cleaved by esterases, aminases, sulphatases and phosphatases, respectively. Pharmacologically active aldehydes are released by the action of esterases and amidases on a variety of compounds that include acyloxyalkyl esters, *N*-acyloxyalkyl derivatives, *N*-Mannich bases derivative, *N*-hydroxymethyl derivatives, and others. In some instances, to facilitate hydrolysis when the prodrug is a poor substrate for the aldehyde-generating enzyme, the carrier is modified with electron withdrawing or donating groups.

[0058] As recognized by those skilled in the art, organic aldehydes undergo a variety of reactions that render the aldehyde chemically protected. By way of non-limiting example, in various embodiments, organic aldehydes are protected by conversion to the corresponding acetal, hemiacetal, aminocarbinol, aminal, imine, enaminone, imidate, amidine, iminium salt, sodium bissulfite adduct, hemimercaptal, dithioacetal, 1,3-dioxepane, 1,3-dioxane, 1,3-dioxalane, 1,3-dioxetane, α-hydroxy-1,3-dioxepane, α-hydroxy-1,3-dioxane, α-hydroxy-1,3-dioxalane, α-keto-1,3-dioxepane, α-keto-1,3-dioxane, α-keto-1,3-dioxalane, α-keto-1,3-dioxetane, macrocyclic ester/imine, macrocyclic ester/hemiacetal, oxazolidine, tetrahydro-1,3-oxazine, oxazolidinone, tetrahydro-oxazinone, 1,3,4-oxadiazine, thiazolidine, tetrahydro-1,3-thiazine, thiazolidinone, tetrahydro-1,3-thiazinone, imidazolidine, hexahydro-1,3-pyrimidine, imidazolidinone, tetrahydro-1,3-pyrimidinone, oxime, hydrazone, carbazone, thiocarbazone, semicarbazone, semithiocarbazone, acyloxyalkyl ester derivative, O-acyloxyalkyl derivative, N-acyloxyalkyl derivative, N-Mannich base derivative, or N-hydroxymethyl derivative. The exemplary schemes in equations 2-12 below also illustrate how many such prodrugs release the active aldehyde *in vivo* (*e.g.*, via hydrolytic or enzymatic hydrolysis).

[0059] In certain embodiments, the protected organic aldehyde is an imine. Those skilled in the art recognize that such derivatives are obtained in a variety of ways, such as, for example, by the methods described by Deaton et al., *Bioorg. Med. Chem. Lett.* 16: 978-983 (2006), or WO2006/012215, by reaction of an organic aldehyde with an amine as in equation 2:



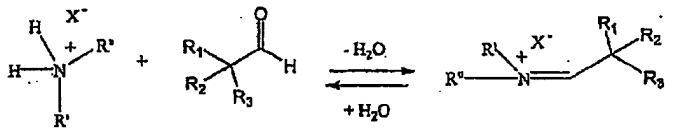
(2)

wherein

each of R_1, R_2 and R_3 is independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2 and cyano; or two or more of R_1, R_2 and R_3 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure; and

R' is selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl.

[0060] In other embodiments, the protected organic aldehyde is an iminium salt. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by the methods described by Paukstelis et al., *J. Org. Chem.* **28**:3021-3024 (1963), by reaction of an organic aldehyde with a secondary amine salt as in equation 3:



(3)

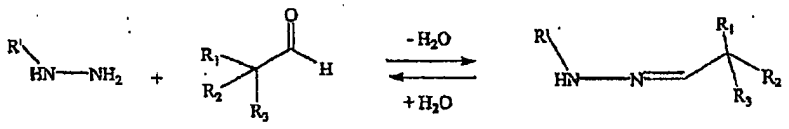
wherein

each of R_1, R_2, R_3 and R' is as defined above with respect to equation 2;

R'' is selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl.;

and X represents any suitable and pharmaceutically acceptable counter anion, such as chloride, bromide, phosphate, carbonate, sulfate, acetate or any other non-toxic, physiologically compatible anion.

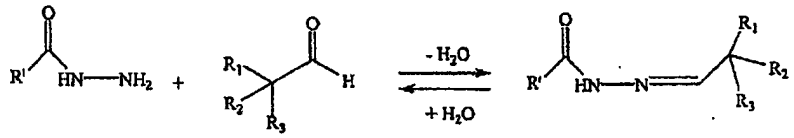
[0061] In another embodiment, the protected organic aldehyde is a hydrazone. Those skilled in the art recognize that such derivatives are prepared in a number of ways such as, for example, by the methods disclosed in U.S. Patent Nos. 6,518,269 and 4,983,755, by reaction of an organic aldehyde with a hydrazine as in equation 4:



(4)

wherein each of R_1, R_2, R_3 and R' is as defined above with respect to equation 2.

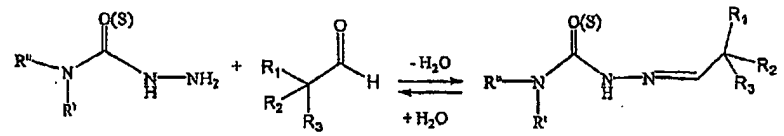
[0062] In yet another embodiment, the protected organic aldehyde is a carbazone. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways such as, for example, using methods described by Herrmann et al., *Chem. Commun.* 2965-2967 (2006) by reaction of an organic aldehyde with a hydrazide (or acyl hydrazine) as in equation 5:



(5)

wherein each of R_1, R_2, R_3 and R' is as defined above with respect to equation 2.

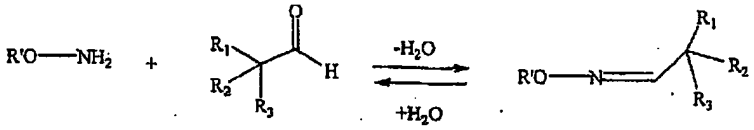
[0063] In another embodiment, the protected organic aldehyde is a semicarbazone or thiosemicarbazone. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, using the methods described by Deaton et al., *Bioorg. Med. Chem. Lett.* 16:978-983 (2006) or by the methods disclosed in U.S. Patent No. 6,458,843, for example, by reaction of an organic aldehyde with a semicarbazine or thiosemicarbazine as in equation 6:



(6)

wherein each of R_1, R_2, R_3, R', R" is as defined above with respect to equations 2 and 3.

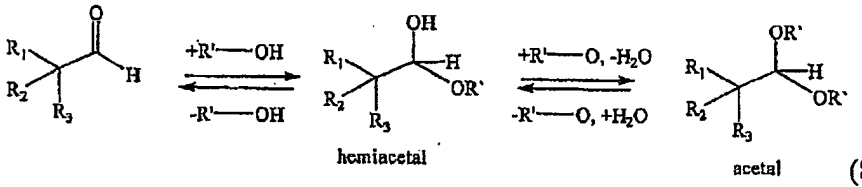
[0064] In still another embodiment, the protected organic aldehyde is an oxime. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, using the methods described by Reymond et al., *Org. Biomol. Chem.* 2:1471-1475 (2004) or U.S. Patent Application No. 2006/0058513, by reaction of an organic aldehyde with an oxoamine as in equation 7:



(7)

wherein each of R_1, R_2, R_3 and R' is as defined above with respect to equation 2.

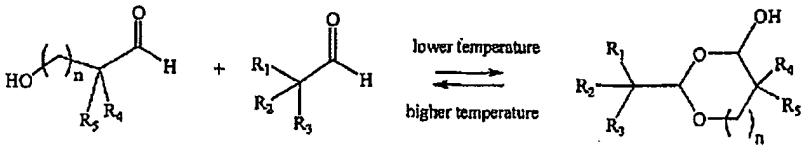
[0065] In another embodiment, the protected organic aldehyde is an acetal or hemiacetal. Those skilled in the art recognize that such derivatives can be prepared in a variety of ways, such as, for example, by reaction of an aldehyde with one or more alcohols as in equation 8:



(8)

wherein each of R_1, R_2, R_3 and R' is as defined above with respect to equation 2.

[0066] In still another embodiment, the protected organic aldehyde is an α-hydroxy-1,3-dioxepane (or α-hydroxy-1,3-dioxane or α-hydroxy-1,3-dioxalane). Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by the methods disclosed in WO03/082850, by reaction of a hydroxy substituted organic aldehyde with another aldehyde, as in equation 9:



(9)

wherein each of R_1, R_2 and R_3 is as defined above with respect to equation 2;

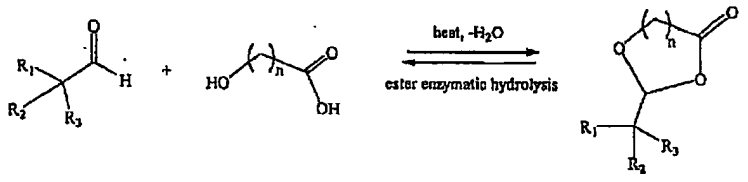
each of R_4 and R_5 is independently selected from H, alkyl, substituted alkyl, cycloalkyl,

substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2 and cyano; or R_4 and R_5 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure; and

n is 1, 2 or 3.

[0067] The reaction shown in equation 9 is an energetically favorable cyclization (dimerization) that occurs spontaneously when the compounds are cooled together (1:1) to room temperature. When heated (*e.g.*, to physiological temperatures), they separate again. Compound 4 is an example of a compound that forms a dimer upon cooling to room temperature.

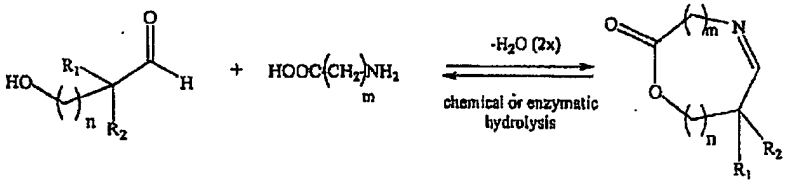
[0068] In yet another embodiment, the protected organic aldehyde is an α-keto-1,3-dioxepane (or α-keto-1,3-dioxane, α-keto-1,3-dioxalane or α-keto-1,3-dioxetane). Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by the methods described by Xu et al., *Tet. Lett.*, 46:3815-3818 (2005) or Krall et al., *Tetrahedron* 61:137-143 (2005), by reaction of an organic aldehyde with a hydroxy acid, thereby forming a protected aldehyde, as in equation 10:



(10)

wherein each of R_1, R_2 and R_3 is as defined above with respect to equation 2; and n is 0, 1, 2, or 3.

[0069] In another embodiment, the protected organic aldehyde is a macrocyclic ester/imine. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, as described in U.S. Patent No. 6,251,927, by reaction of a hydroxy substituted organic aldehyde with a compound of the formula $HOOC\text{-}(CH_2)_m\text{-}NH_2$, thereby forming a protected aldehyde, as in equation 11:

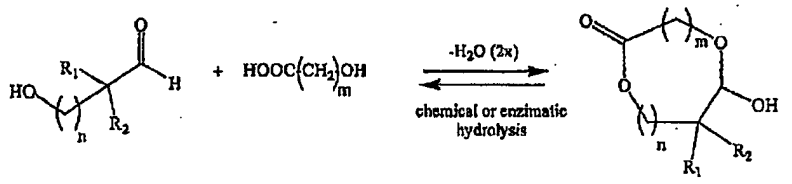


(11)

wherein R_1 and R_2 are as defined above with respect to equation 2; n is 0, 1, or 2; and m is 1 or 2.

[0070] Hydrolysis of the compound formed in equation 11 occurs by chemical hydrolysis through the imine, or enzymatic hydrolysis through the ester group.

[0071] In another embodiment, the protected organic aldehyde is a macrocyclic ester/hemiacetal. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, as described in U.S. Patent No. 6,251,927 by reaction of a hydroxy substituted organic aldehyde with a hydroxy acid having the structure $HOOC\text{-}(CH_2)_m\text{-}OH$, thereby forming a protected aldehyde, as in equation 12:



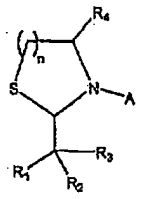
(12)

wherein R_1, R_2, m and n are as defined above with respect to equation 11.

[0072] Hydrolysis of the compound formed in equation 12 occurs by chemical hydrolysis through the ketal, or enzymatic hydrolysis through the ester group.

[0073] In still another embodiment, the protected organic aldehyde is a thiazolidine or a tetrahydro-1,3-thiazine. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Jellum et al., *Anal. Biochem.* **31**:339-347 (1969), Nagasawa et al., *J. Biochem. Mol. Tox.* **16**:235-244 (2002), Roberts et al., *Chem. Res. Toxicol.* **11**:1274-82 (1998) or U.S. Patent No. 5,385,922. Certain

thiazolidines and tetrahydro-1,3-thiazines contemplated for use as described herein are represented by formula II:



(II)

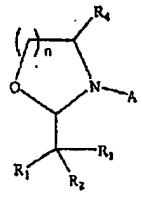
wherein

each of R_1, R_2, R_3 and R_4 is independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2, and cyano; or two or more of R_1, R_2 and R_3 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure;

A is selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl and alkylsulfinyl; and

n is 1 or 2.

[0074] In another embodiment, the protected organic aldehyde is an oxazolidine or a tetrahydro-1,3-oxazine. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Bundgaard et al., *Int. J. Pharma. Chem.* **10**:165-175 (1982), Sélambarom et al., *Tetrahedron* 58:9559-9556 (2002) or U.S. Patent No. 7,018,978. Certain oxazolidines and tetrahydro-1,3-oxazines contemplated for use as described herein are represented by formula III:

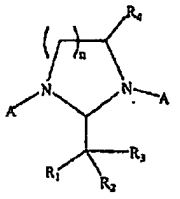


(III)

wherein each of R_1, R_2, R_3, R_4 and A and n is as described above with respect to formula II.

[0075] In still another embodiment, the protected organic aldehyde is an imidazolidine or a

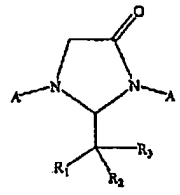
1,3-hexahydro-pyrimidine. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Lambert, *J. Org. Chem.* 52:68-71 (1987) or Fülöp, *J. Org. Chem.* 67:4734-4741 (2002). Certain imidazolidines and 1,3-hexahydro-pyrimidines contemplated for use as described herein are represented by formula IV:



(IV)

wherein each of R_1, R_2, R_3, R_4, n and A (selected independently at each occurrence) is as described above with respect to formula II.

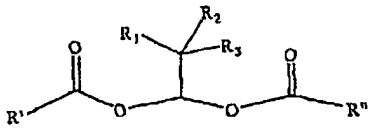
[0076] In yet another embodiment, the protected organic aldehyde is an imidazolidinone. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Bundgaard et al., *Int. J. Pharma. Chem.* 23:163-173 (1985). Certain imidazolidinones contemplated for use as described herein are represented by formula V:



(V)

wherein each of R_1, R_2, R_3 and A (selected independently at each occurrence) is as described above with respect to formula II.

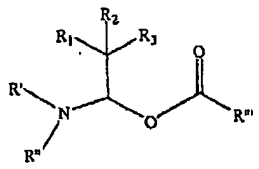
[0077] In another embodiment, the protected organic aldehyde is an acyloxyalkyl ester or O-acyloxyalkyl derivative. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Nudelman et al., *Eur J. Med. J. Chem.* 36: 63-74 (2001), Nudelman et al., *J. Med. Chem.* 48:1042-1054 (2005), or Swedish Patent No. SE9301115. Certain acyloxyalkyl esters contemplated for use as described herein are represented by formula VI:



(VI)

wherein each of R_1, R_2, and R_3 is as defined above with respect to formula II, and each of R' and R" is selected independently from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl. In certain embodiments, in addition to releasing the active aldehyde upon metabolic hydrolysis *in vivo*, an acyloxyalkyl ester derivative also releases butyric acid. Butyric acid prodrugs have been reported to provide increased aqueous solubility and permeability across cell membranes (Nudelman et al., *Eur J. Med. J. Chem.* 36: 63-74 (2001)).

[0078] In another embodiment, the protected organic aldehyde is an N-acyloxyalkyl derivative. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Bundgaard et al., *Int. J. Pharm.* 22:454-456 (1984) and Bundgaard et al., *Int. J. Pharm.* 13:89-98 (1983). Certain N-acyloxyalkyl derivatives contemplated for use as described herein are represented by formula VII:



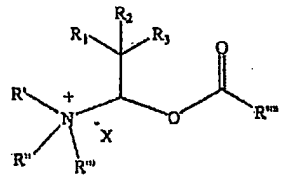
(VII)

wherein each of R_1, R_2, R_3, R' and R" is as described above with respect to formulas II and VI;

and R"' is selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

[0079] In another embodiment, the protected organic aldehyde is the salt of an

N-acyloxyalkyl derivative. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Bodor et al., *J. Med. Chem.* 23:469-474 (1980) or U.S. Patent No. 3,998,815. The salts of N-acyloxyalkyl derivatives contemplated for use as described herein are represented by formula VIII:



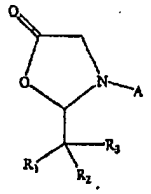
(VIII)

wherein each of R_1, R_2, R_3, R', R'', and R''' is as defined above with respect to formula VII;

R'''' is selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

X represents a suitable and pharmaceutically acceptable counter anion, as described above with respect to equation 3.

[0080] In yet another embodiment, the protected organic aldehyde is a 5-oxazolidinone. Those skilled in the art recognize that such derivatives can be obtained in a variety of ways, such as, for example, by employing the methods described by Bundgaard et al., *Int. J. Pharma. Chem.* 46:159-167 (1988) or Ishai-Ben, *J. Am. Chem. Soc.* 79:5736-38 (1957). Certain 5-oxazolidinones contemplated for use as described herein are represented by formula IX:



(IX)

wherein each of R_1, R_2, R_3 and A is as defined above with respect to formula II.

[0081] The organic aldehydes and their derivatives disclosed herein are administered to treat inflammatory disease in animals, such as mammals, including but not limited to human patients. "Inflammatory disease" as used herein refers to a disease or condition characterized by inflammation. Inflammation encompasses the first response of the immune system to infection or irritation, and is sometimes referred to as the innate cascade. Inflammation typically is characterized by one or more of the following symptoms: redness, heat, swelling, pain, and dysfunction of the organs involved. "Treatment" as used herein encompasses prevention of a

disease or its progression, reduction of one or more symptoms (e.g., pain) associated with a disease or condition, and/or amelioration or curing of the underlying disease state or condition. An "anti-inflammatory effective amount" of an aldehyde or its derivative is an amount sufficient for treatment of an inflammatory disease.

[0082] Examples of inflammatory diseases treatable as described herein include without limitation transplant rejection; chronic inflammatory disorders of the joints, such as arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung disorders, such as asthma, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD) or chronic obstructive airway disease; inflammatory disorders of the eye, such as corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disorders of the gum, such as gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, such as uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the liver, such as viral hepatitis and autoimmune hepatitis; inflammatory disorders of the skin, such as sclerodermatitis, psoriasis, erythema, eczema, or contact dermatitis; inflammatory diseases of the central nervous system, such as stroke, chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, such as diabetes mellitus, immune-complex vasculitis, systemic lupus erythematosus (SLE); inflammatory diseases of the heart, such as cardiomyopathy, ischemic heart disease, hypercholesterolemia, and atherosclerosis; as well as inflammation resulting from various diseases such as preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. Inflammatory diseases treatable as described herein further include systemic inflammations of the body. Examples of systemic inflammation include but are not limited to gram-positive or gram negative shock, sepsis, septic shock, hemorrhagic or anaphylactic shock, and systemic inflammatory response syndrome. Further examples of inflammatory disease include circulatory shock, hemorrhagic shock and cardiogenic shock.

[0083] In one embodiment, the inflammatory disease is a chronic inflammatory disease, such as rheumatoid arthritis. In another embodiment, the inflammatory disease is a disease associated with a chronic inflammatory reaction, such as atherosclerosis or Alzheimer's disease; or with

ischemia/reperfusion injury, such as myocardial infarction, stroke, sleep apnea or transplantation. In one embodiment, the inflammatory disease is an infectious disease, such as septic shock.

[0084] The organic aldehydes and their derivatives disclosed herein are formulated into pharmaceutical compositions for administration to treat inflammatory disease. In certain embodiments, the compositions include a pharmaceutically acceptable salt of the aldehyde or derivative, for example, a pharmaceutically acceptable salt of a compound having the general formula I above. Those skilled in the art understand the use of pharmaceutically acceptable salt forms of compounds in formulating pharmaceutical compositions. The compositions are administered in a variety of forms, adapted to the chosen route of administration. Suitable routes of administration include without limitation oral, rectal, transdermal, topical, and parenteral, *e.g.*, intravenous (i.v.), subcutaneous, intramuscular, intrapleural, intraperitoneal, intrafocal and perifocal administration.

[0085] The pharmaceutical compositions typically contain an organic aldehyde or its derivative as disclosed herein, or a pharmaceutically acceptable salt thereof, as an active agent in a non-toxic, pharmaceutically acceptable vehicle. In certain embodiments, the composition is an admixture of the active agent and a carrier in solid, semisolid, or liquid form. In some embodiments, the active agent is provided in an encasing composition, for example, a capsule, a tablet coating, a bag, or some other container for the active agent. In certain embodiments, the vehicle includes one or more additional formulating agents, flavoring agents, coloring agents, or preservatives.

[0086] Suitable compositions for oral administration include, for example, tablets, dragees, capsules, pills, powders, troches, granules, suspensions, emulsions, solutions, syrups and elixirs. In certain embodiments, the pharmaceutical composition is a solid dosage form including a carrier that contains at least one inert diluent, such as, for example, sucrose, lactose or starch. In some instances, such carriers also include one or more additional formulating substances, *e.g.*, lubricating agents such as magnesium stearate. In some embodiments, capsules, tablets, troches or pills are prepared with a carrier that also includes one or more buffering agents. In certain embodiments, vehicles such as tablets, pills, or granules are prepared with enteric coatings.

[0087] In certain embodiments, tablets are prepared including the active agent and one or more of the following: an inert diluent, such as, for example, calcium carbonate, calcium phosphate, sodium phosphate, or lactose; a granulation or distributing agent, such as corn starch or alginate; a binder, such as amylose, gelatin, or acacia gum; and a lubricant, such as aluminum stearate, magnesium stearate, talc, or silicone oil. In some embodiments, tablets are provided

with a coating that effects a delayed dissolution and reabsorption of the active agent in the gastrointestinal tract and thus, for example, provides improved compatibility or a longer duration of effectiveness. In certain embodiments, gelatin capsules are prepared containing the active agent in a mixture with a solid diluent (*e.g.*, calcium carbonate or kaolin), or an oily diluent (*e.g.*, olive, peanut, or paraffin oil).

[0088] In certain embodiments, liquid dosage forms are prepared with inert diluents commonly used in the art, such as water. In some instances such compositions further include one or more additional components including adjuvants, such as dispersing and wetting agents, emulsifying and suspending agents, sweetening and flavoring agents, and/or preservatives. Suitable suspension agents include, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, sodium alginate, polyvinylpyrrolidone, tragacanth gum and acacia gum. Non-limiting examples of suitable dispersing and wetting agents include polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylene, sorbitol monooleate, polyoxyethylene sorbitan monooleate or lecithin. Suitable preservatives include, for example, methyl or propyl hydroxybenzoate. Non-limiting examples of suitable flavoring agents and sweeteners include sucrose, lactose, dextrose or sugar syrup.

[0089] In some embodiments, oily suspensions are prepared including, for example, peanut, olive, sesame, coconut, or paraffin oil, and optionally one or more thickeners, such as beeswax, hard paraffin or cetyl alcohol, sweeteners, flavoring agents and/or anti-oxidants. In certain embodiments, emulsions are prepared including, for example, olive, peanut, or paraffin oil in addition to one or more emulsifiers, such as acacia gum, tragacanth gum, phosphatides, sorbitan monooleate or polyoxyethylene sorbitan monooleate, and optionally one or more sweeteners and/or flavoring agents. In other embodiments, water dispersible powders or granules are prepared containing the active agent in a mixture with one or more dispersing, wetting, or suspension agents, *e.g.*, the aforementioned materials and/or dimethyl sulfoxide, as well as optionally one or more sweeteners, flavoring agents and/or coloring agents.

[0090] In certain embodiments, the organic aldehydes are administered parenterally as sterile isotonic sodium chloride solutions or other solutions. In some instances, to promote uniform dissolution or suspension, a solubilizer is added, such as dimethyl sulfoxide. Pharmaceutically acceptable carriers for intravenous administration include, without limitation, solutions containing pharmaceutically acceptable salts or sugars. Pharmaceutically acceptable carriers for intramuscular or subcutaneous injection include, without limitation, salts, oils, or sugars. In some instances, carriers such as solvents, water, buffers, alkanols, cyclodextrins and aralkanols

are used. Other optional auxiliary, non-toxic ingredients include, for example, polyethylene glycols or wetting agents. In certain embodiments, an injectable solution is formulated with a buffer such as, for example, sodium bicarbonate or tris(hydroxymethyl)aminomethane. In at least some instances, the formulation has a pH between about 4 and about 7, for example, between about 5.0 and about 5.5.

[0091] Pharmaceutically acceptable carriers for preparing compositions for topical administration include, without limitation, dimethyl sulfoxide, alcohol, and propylene glycol. In some instances, topical compositions are applied using patches or other liquid retaining material to hold the pharmaceutical composition in contact with the skin.

[0092] Suitable compositions for rectal administration include, without limitation, suppositories produced with one or more binders that melt at rectal temperature, for example, cocoa butter or polyethylene glycols.

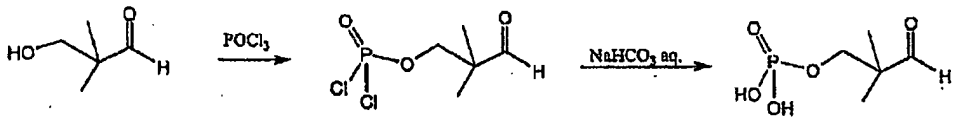
[0093] In some embodiments, the organic aldehyde composition is formulated to provide sustained release or delayed release. In certain embodiments, carriers based on nanoparticles or nanoencapsulates are used, *e.g.*, to protect the active agent and provide for its slow release in the organism or specific tissues.

[0094] In certain embodiments, the organic aldehydes and their derivatives disclosed herein are administered concomitantly with another active agent, such as another anti-inflammatory or immunosuppressive drug, including but not limited to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), steroids or methotrexate and other disease modifying anti-rheumatic drugs (DMARDs). In various embodiments, the multiple active agents are administered as part of a single dosage form, or in multiple dosage forms administered at the same time or at different times.

[0095] In some instances, the organic aldehyde is linked to a second therapeutic agent such as, for instance, an anti-inflammatory agent. In certain embodiments, the second agent is selected based on its known capacity to target the site/tissue in which a therapeutic effect is desired. For example, in some embodiments, an anti-inflammatory agent is selected for its known capacity to accumulate in an inflammatory lesion. Anti-inflammatory drugs that accumulate in inflamed tissues include, without limitation, aspirin, indomethacin, and other nonsteroidal anti-inflammatory drugs that are organic acids. In other embodiments, the organic aldehyde is targeted to a particular tissue or cell type by linking it to a protein carrier. Carrier proteins include but are not limited to antibodies specific for a cell surface protein or a component of the extracellular matrix. In certain embodiments, the aldehyde is linked to an

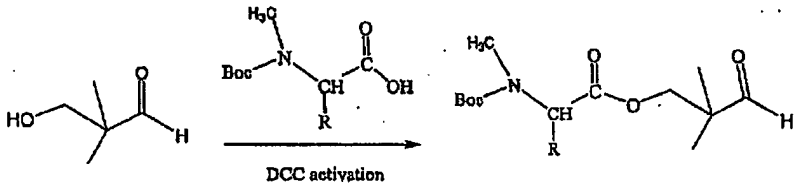
amino acid such as, for example, cysteine. In still other embodiments, an aldehyde is derivatized to target the bones by introducing a phosphonic acid moiety.

[0096] Equation 13 illustrates a reaction scheme for introduction of a phosphonic acid moiety to 3-hydroxy-2,2-dimethylpropanal (compound 4). In the illustrated embodiment, the phosphonic acid is introduced using $POCl_3/Et_3N$ followed by basic hydrolysis.



(13)

[0097] Equation 14 illustrates a reaction scheme for introduction of an amino acid, through the acid function, to 3-hydroxy-2,2-dimethylpropanal (compound 4). In the illustrated embodiment, the *N*-protected amino acid (*e.g.*, *N*-Boc-glycine) with DCC (dicyclohexylcarbodiimide) activation reacts with the hydroxyl function.



(14)

[0098] The active agent content in the pharmaceutical compositions is ordinarily about 0.01% to about 95% by weight, for example, about 0.1% to about 85% by weight, about 1% to about 70% by weight, or about 5% to about 50% by weight, based on the final pharmaceutical formulation. In various embodiments, the desired daily dose is administered in a single dose, or as divided doses at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be divided further into a number of discrete loosely spaced administrations. When administered in a unit dosage form, the pharmaceutical compositions typically contain between about 1 mg and about 10,000 mg, for example, between about 5 mg and about 7,500 mg, between about 10 mg and about 2,000 mg, between about 20 mg and about 1,000 mg, between about 20 mg and about 500 mg, or between about 20 mg and about 300 mg of active agent. In certain embodiments, an aldehyde or its derivative is administered in a daily dose ranging between about 1 mg and about 20,000 mg, for example, between about 5 mg and about 10,000 mg, between about 10 mg and about 5,000 mg, between about 20 mg and about

1,000 mg, between about 40 mg and about 500 mg, or between about 40 mg and about 300 mg of active agent.

[0099] The dosage level of active agent in the composition is chosen to provide an amount of active agent that affords the desired therapeutic effect in accordance with the desired method of administration. As those skilled in the art appreciate, the amount of the composition required for use in treatment varies not only with the particular compound selected, but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will be ultimately at the discretion of the attendant physician.

[0100] In certain embodiments, useful dosages of organic aldehyde compositions are determined by assessing their *in vitro* activity and *in vivo* activity in animal models. Methods for extrapolation of effective dosages in mice and other animals to humans are known to those skilled in the art. (See, *e.g.*, U.S. Patent No. 4,938,949 and National Institute of Environmental Health Sciences, U.S. Public Health Service, Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity.)

[0101] The therapeutic aldehydes disclosed herein generate CO after administration to the body. Although in at least some instances CO is generated preferentially at sites of inflammation, some of the CO generated will bind to hemoglobin in red blood cells. Thus, dose-finding studies can be guided by measurement of carboxyhemoglobin (COHb) levels in the blood. Methods for the measurement of COHb levels in the blood are known in the art. In normal healthy humans, COHb levels are about 0.5% in healthy nonsmokers and up to 9% in smokers. In one embodiment, the dose level of the compositions described herein is such that no significant rise in COHb levels is observed. However, in some applications, a transient rise in COHb levels up to about 10% may be tolerated. This level of COHb is not associated with any symptoms.

Examples

[0102] The following examples are illustrative only, and are not intended to be limiting. The following definitions are used herein. "RPMI" is an aqueous tissue culture medium developed by Moore et. al at Roswell Park Memorial Institute (commercially available from Sigma). The abbreviation rpmi is used for RPMI-1630 media supplemented with 10% fetal calf serum. "TBHP" refers to tert-butyl hydroperoxide, T-HYDRO® solution, 70% wt in water. "H_2O_2," refers to hydrogen peroxide solution, 35% in water. "pH 2" refers to an aqueous solution with pH between 2 and 2.5. "Eq." refers to the number of equivalents of carbon monoxide.

Example 1: CO release from trimethylacetaldehyde (compound 1) in different media

[0103] A sample of commercially available (*e.g.*, from Aldrich) trimethylacetaldehyde (compound 1) was placed in a 7.5 ml vial and then sealed with an appropriate stopper. In each experiment 2 ml of the appropriate solution, TBHP, H_2O_2, rpmi or pH 2 solution, was added and the vial placed at 37°C with orbital stirring.

[0104] At the appropriate time, 250 µl of the gas mixture was removed from the vial, injected in the gas chromatograph (Trace GC with a TCD detector from Thermo Finnigan, connected to a Chrom-card 32 bit software), and the amount of CO was measured according to previously calibrated conditions.

[0105] As shown in Figure 1, trimethylacetaldehyde released CO in TBHP solution, and very little in acidic aqueous solution. In both cases, the CO release was inhibited by the addition of a radical trap, 2,6-di-tert-butylphenol, thus confirming a radical decarbonylation mechanism. Figure 1A shows CO release from trimethylacetaldehyde at a concentration of 0.11M. No CO was detected in the rpmi or hydrogen peroxide solutions.

[0106] The amount of CO released in TBHP solution varied with the concentration of both trimethylacetaldehyde and TBHP. The CO released by trimethylacetaldehyde increased with the concentration of TBHP until approximately eight equivalents of TBHP was reached. For concentrations up to 32 eq. of TBHP the CO release was maintained. When the concentration of TBHP was reduced to values known to exist in inflamed tissues, such as 1 mM, CO release still was observed. There was also a pronounced effect related to the concentration of trimethylacetaldehyde: the maximum CO release was obtained for concentrations around 0.12M, and CO release decreased approximately to half at higher and lower concentrations of 0.25 M and 0.08 M, respectively. Figure 1B shows CO release at varying trimethylacetaldehyde concentrations in 1.9 M TBHP. Figures 1C-D show CO release from trimethylacetaldehyde at a concentration of 0.23 M in varying concentrations of TBHP.

Example 2: CO release from 2,2-dimethyl-4-pentenal (compound 2) in different media

[0107] A sample of the commercially available (*e.g.*, from Aldrich) 2,2-dimethyl-4-pentenal (compound 2), was placed in a 7.5 ml vial and sealed with an appropriate stopper, and the experiments were performed as described above in Example 1.

[0108] As shown in Figure 2, 2,2-dimethyl-4-pentenal (0.16 M) released CO in the TBHP

solution, very little at pH 2, and even less in rpmi. No CO release was observed in H_2O_2 solution.

Example 3: CO release from 4-ethyl-4-formyl-hexanenitrile (compound 3) in different media

[0109] A sample of the commercially available (from Acros Organic) 4-ethyl-4-formyl-hexanenitrile (compound 3), was placed in a 7.5 ml vial and sealed with an appropriate stopper, and the experiments were performed as described above in Example 1.

[0110] As shown in Figure 3, 4-ethyl-4-formyl-hexanenitrile (0.15 mM) released a very high amount of CO in TBHP, less at pH 2, and even less in rpmi. No CO release was observed in H_2O_2 solution.

Example 4: Preparation of 3-hydroxy-2,2-dimethylpropanal (compound 4) and CO release from 3-hydroxy-2,2-dimethylpropanal in different media

[0111] The preparation of 3-hydroxy-2,2-dimethylpropanal (compound 4) was performed according to the methods described by Santoro et al., *J. Chem. Soc. Perkin Trans. I* 189-192 (1978).

[0112] To a mixture of 2-methylpropionaldehyde (690 mmol) and formaldehyde (37 wt% solution in water) (747 mmol, 1.1 eq.) at 0 °C was added potassium carbonate (290 mmol, 0.42 eq.) portionwise in order to keep the temperature below 20 °C. After stirring for 2 hours at room temperature, the reaction mixture was extracted with diethyl ether, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled to afford 3-hydroxy-2,2-dimethylpropionaldehyde, b.p. 65°C (15 mmHg). On cooling to room temperature, the corresponding dimer was formed as a white solid in 52 % yield. IR ν (cm^{-1}) 3434, 3316, 3222, 3297, 2886, 1475, 1363, 1234, 1118, 1051, 977, 892, 790, 701. Elemental analysis Exp (Calc) C: 58.33 (58.82), H: 10.33 (9.80).

[0113] A sample of 3-hydroxy-2,2-dimethylpropanal (compound 4), was placed in a 7.5 ml vial and sealed with an appropriate stopper, and the experiments were performed as described above in Example 1.

[0114] 3-hydroxy-2,2-dimethylpropanal (0.12 M) released CO only in TBHP solution. As shown in Figure 4, initially the CO release was small, but within one day, it reached high levels. This was understood to occur because the dimer initially present in solution equilibrated to the monomer, which was able to generate CO.

Example 5: Preparation of 2-formyl-2-methyl-propylmethanoate (compound 5) and CO release from 2-formyl-2-methyl-propylmethanoate in different media

[0115] The preparation of 2-formyl-2-methyl-propylmethanoate (compound 5) was performed according to the methods described by Effenberger et al., *Tetrahedron: Assymetry*, 6:271-282 (1995).

[0116] A solution of hydroxypivaldehyde freshly melted was dissolved in dichloromethane and toluene (1/5 of the total volume) with a final concentration of 0.3 M. The solution was placed in a 40 °C bath to make sure that only the monomer was in solution, and pyridine was added (1.5 eq.) followed by acetic anhydride (3 eq.). The mixture was stirred at 60 °C for 40 hours. Then the reaction mixture was filtered through a short pad of silica gel (5x 3 cm) and eluted with dichloromethane to remove the salts. The filtrate was evaporated and the residue was fractionally distilled in vacuo. (bp 75 °C/10 Torr). Yield 55%. IR (cm^{-1}) ν (cm^{-1}) 2981, 1745, 1477, 1378, 1243, 1045, 682; ^1H NMR (300 MHz) δ ppm 9.52 (s, 1H, CHO), 4.12 (s, 2H, CH_2), 2.05 (s, 3H, CH_3CO_2), 1.12 (s, 6H, CH_3).

[0117] A sample of 2-formyl-2-methyl-propylmethanoate (compound 5), was placed in a 7.5 ml vial and sealed with an appropriate stopper, and the experiments were performed as described above in Example 1.

[0118] 2-Formyl-2-methyl-propylmethanoate (0.17 M) released CO only in TBHP solution and, as shown in Figure 5, when compared to the compounds tested in the other Examples, released the lowest amount of CO.

Example 6: Preparation of 2,2-dimethyl-3-(p-methylphenyl)propanal (compound 6) and CO release from 2,2-dimethyl-3-(p-methylphenyl)propanal in different media

[0119] The preparation of 2,2-dimethyl-3-(p-methylphenyl)propanal (compound 6) was performed according to the methods described in European Patent No. 0076493.

[0120] A solution of potassium hydroxide (224 g, 4 mol) and 10 g of ALIQUAT 336 (tricapryl-methyl-ammonium chloride) was stirred in 125 ml of water and 200 ml of toluene and heated to boiling. With continuing boiling, a solution of benzyl chloride (402 g, 3.2 mol) and isobutyraldehyde (256 g, 3.6 mol) was added dropwise. After 14 hours of stirring at boiling temperature, the solution was cooled down to room temperature and diluted with 300 ml of water. The aqueous phase was extracted with diethyl ether. The combined organic phases were

washed and concentrated. The crude product (yellow oil) gave after distillation over a fractionated column a colourless oil. Yield 69 %. IR ν (cm^{-1}) = 2977, 2933, 2727, 1729, 1515, 1463, 1201, 819; ^{1}H-NMR: δ = 9.51 (s, 1H, CHO), 6.92 (d, J =1.8, 2H, Ar), 6.89 (d, J = 1.8, 2H, Ar), 2.67 (s, 2H, CH_2), 2.24 (s, 3H, Ph-CH_3), 0.97 (s, 6H, 2xCH_3).

[0121] A sample of the 2,2-dimethyl-3-(*p*-methylphenyl)propanal (compound 6), was placed in a 7.5 ml vial, sealed with an appropriate stopper, and the experiments were performed as described above in Example 1.

[0122] As shown in Figure 6, 2,2-dimethyl-3-(p-methylphenyl)propanal (0.14 M) released CO in all media tested except H_2O_2 solution.

Example 7: Preparation of 2-methyl-2-phenylpropionaldehyde (compound 7) and CO release from -methyl-2-phenylpropionaldehyde in different media

[0123] The preparation of 2-methyl-2-phenylpropionaldehyde (compound 7) was performed according to the methods described by Goto et al., *J. Inorg. Biochem.* 69:241-247 (1988). To a THF (200 ml) suspension of sodium hydride (7.2 g, 193 mmol) (60% oil dispersion) cooled in an ice bath was added dropwise 2-phenylpropionaldehyde (24 ml, 179 mmol). After stirring for 10 minutes, iodomethane (12 ml, 193 mmol) in THF (10 ml) was added dropwise, and the solution turned progressively yellow. The mixture was stirred at room temperature overnight and kept away from light. The next day, water (20 ml) was added and the resultant THF/aqueous solution was extracted three times with diethyl ether (3 x 100 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated. The remaining yellow liquid was purified by distillation under reduced pressure (20 mmHg, 82-85 °C) to give a colourless oil in 63 % yield. IR ν (cm^{-1}) = 3457, 2979, 2816, 2711, 1602, 1497, 1253, 1030, 838, 701; ^{1}H-NMR: δ = 9.51 (s, 1H, CHO), 7.20-7.40 (m, 5H, Ar), 1.47 (s, 6H, 2 x CH_3).

[0124] A sample of 2-methyl-2-phenylpropionaldehyde (compound 7) was placed in a 7.5 ml vial, sealed with an appropriate stopper, and the experiments were performed as described above in Example 1.

[0125] As shown in Figure 7, 2-methyl-2-phenylpropionaldehyde (0.16 M) released CO in all media tested except rpmi solution.

[0126] Figures 8 and 9 summarize the kinetics of CO release for the aldehydes tested as described in Examples 1-7. As illustrated in Figure 9, the aldehydes showed different CO release abilities. They all released CO in the presence of tert-butyl-hydroperoxide medium

(TBHP) (Figure 8). TBHP was always present in excess, above 16 equivalents. As explained above in Example 1, the excess TBHP did not affect CO release for concentrations above 8 equivalents. TBHP is a very efficient radical initiator that abstracts the hydrogen atom of the aldehydic function, and initiates the radical decarbonylation process (Berman et al., *J. Am. Chem. Soc.* 85:4010-4013 (1963)). The same did not occur in the hydrogen peroxide medium (H_2O_2), a less efficient radical initiator, where only compound 7 responded significantly to decarbonylation. Compound 7 was expected to be more reactive, because decarbonylation produces a more stable tertiary radical, stabilized by both resonance hyperconjugation and conjugation.

[0127] Compounds 3, 6 and 7 decarbonylated significantly in acidic aqueous solutions. It is known that some aromatic aldehydes can decarbonylate in acidic media through an ionic mechanism (Bukket, *J. Am. Chem. Soc.* 81:3924 (1959)), and the same could happen for compounds 3, 6 and 7. However, the addition of a radical trap, 2,6-di-tert-butylphenol, inhibited the decarbonylation process, thus suggesting a radical mechanism. The same is true for the decarbonylation in rpmi observed for compounds 2, 3 and 6.

[0128] Experiments on CO release in various media as described in Examples 1-7 are useful for predicting how aldehydes will behave *in vivo*. For example, testing the CO release in different media as illustrated allows for the identification of aldehydes that selectively release CO in the presence of reactive oxygen species (*e.g.*, represented by H_2O_2 and TBHP, the latter being more reactive), but do not release CO in a general aqueous environment under normal physiological conditions (*e.g.*, represented by rpmi (plasma) and pH 2 (stomach)). Reactive oxygen species are known to exist in inflamed tissues at concentrations of about 1 mM (B. Halliwell & J.M.C. Gutteridge, *Free Radicals in Biology and Medicine*, Oxford University Press, 3rd Ed., 1999).

Example 8: Anti-arthritic activity of compounds 1 and 2

[0129] Adjuvant arthritis was induced in outbred Sprague-Dawley rats by intradermal injection into the subplantar area of the right hind paw of 0.1 ml of a 10 mg/ml suspension of Mycobacterium butyricum, killed and dried in Freund's incomplete adjuvant. Treatment was initiated 10 days after disease induction at the time of disease onset. Groups of 7 rats received intraperitoneal injections of compound 1 and compound 2 in 1 ml PBS, each at a dose of 100 mg/kg/day for 20 days. A control group of 7 rats received no treatment. Progression of arthritis

was monitored by daily measurements of right and left paw volumes by a water displacement method using a plethysmometer, by daily measurements of the ankle circumference with a flexible strip, and by determination of the arthritic index based on levels of erythema and oedema of the entire paws and digits, number of joints involved, spondylosis, lesions on the tail, movement capacity and infections. The maximum possible score was 11.

[0130] As shown in Figure 10, untreated control rats lost body weight after the onset of the disease on day 10 after disease induction. No loss of body weight was observed in the rats treated with compounds 1 and 2. Both compounds also prevented the increase in paw volume and circumference that was observed in untreated control rats (Figures 11A (right paw volume), 11B (left paw volume), 11C (right paw circumference) and 11D (left paw circumference)). The arthritic index reached values above 8 in untreated rats, and remained below 3 in the treated animals (Figure 12).

Example 9: Anti-arthritic activity of compounds 1 and 7

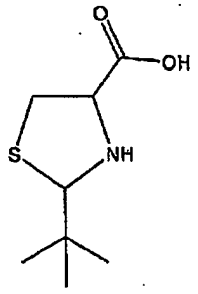
[0131] Adjuvant arthritis was induced in Lewis rats by a single intradermal injection (0.1 ml) of heat killed Mycobacterium tuberculosis H37Ra (0.3 mg) in Freund's incomplete adjuvant into the right footpad. Treatments were initiated at day 10 after disease induction, and consisted of daily injections for 30 consecutive days. Groups of 11 rats were treated with compound 1 (100 mg/kg), compound 1 (25 mg/kg), compound 7 (100 m/kg), compound 7 (25 mg/kg), vehicle (carboxymethyl cellulose, 0.5% and Tween 80 (polyoxyethylene-20 sorbitan monooleate), 0.5%), dexamethasone (DEX, a glucocorticoid anti-inflammatory agent, 0.3mg/kg), and one group remained untreated. The body weight was determined daily. The course of the disease was monitored by measurement of paw volume using plethysmometry on a weekly basis, and by macroscopic assessment of the levels of erythema and oedema of the entire paws and digits and number of joints involved. The arthritic index was calculated for each rat by adding the 4 scores of individual paws.

[0132] As shown in Figure 13, the increase in body weight of untreated rats was 45.7% by day 40 of the study. The increase in body weight of rats treated with compound 7 (100 mg/kg), compound 7 (25 mg/kg), and dexamethasone was 31.6%, 28.6%, and 25.7%, respectively. The increase in body weight of rats treated with compound 1 (100 mg/kg) and compound 1 (25 mg/kg) was 40% and 38.7%, respectively. This increase in the latter groups was similar to that observed in vehicle treated rats (36.8%).

[0133] Treatment with compounds 1 and 7 reduced the increase in paw volume as compared to treatment with vehicle or with untreated rats (Figure 14). This effect was significant from day 28 on. The reduction in paw volume in rats treated with compound 7 (100 mg/kg) was comparable to that seen in rats treated with dexamethasone. The arthritic score was only slightly influenced, and not in a continuous fashion, by the treatment with compound 1 and compound 7 (Figure 15). A significant inhibition of arthritic score relative to vehicle treated rats was observed on days 14, 18, 28, 30 and 36 for compound 1 (100 mg/kg), on days 16 and 30 for compound 1 (25 mg/kg), on day 14 for compound 7 (100 mg/kg) and on days 14 and 28 for compound 7 (25 mg/kg).

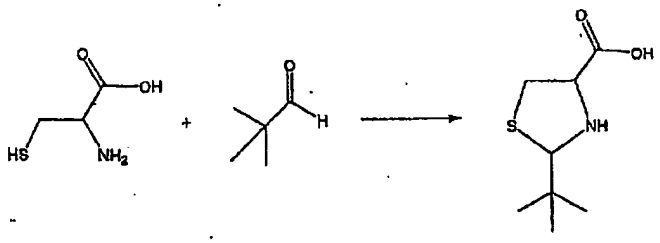
Example 10: Preparation of 2-*tert*-butyl-thiazolidine-4-carboxylic acid (compound 9) and CO release from 2-*tert*-butyl-thiazolidine-4-carboxylic acid in TBHP

[0134] 2-*tert*-butylthiazolidine-4-carboxylic acid (compound 9)



(9)

was synthesized and tested for CO release in TBHP. The compound was prepared as illustrated in equation 15:



(15)

Specifically, the preparation of 2(RS)-*tert*-butyl-thiazolidine-4(R)-carboxylic acid was performed by a method related to that described by Nagasawa et al., *J. Biochem. Mol. Tox.* 16:235-244 (2002). L-cysteine (3.28 g) and trimethylacetaldehyde (3.56 ml, 1.2 eq) were mixed in 40 ml of methanol. The solution was stirred for 5 hours at room temperature, and the solvents evaporated to yield a white powder. Elemental analysis Exp (Calc) C: 50.89 (50.76); H: 7.96

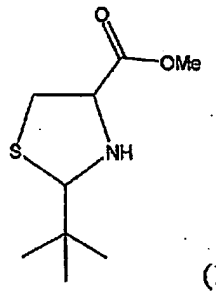
(7.99); N 7.46 (7.40); S 17.33 (16.94); IR ν (cm^{-1}) = 3455, 3065, 2966, 1644, 1481, 1360, 1305, 1202, 859, 619; ^{1}H-NMR (D_2O) δ: 4.71(d, J = 1.2 Hz, 0.4H, S-CH-NH), 4.64 (d, J =0.6 Hz, 0.6H, S-CH-NH), 4.58-4.57 (m, 0.4H, CH_2-CH-NH), 4.3-4.29 (m, 0.6H, CH_2-CH-NH), 3.30 (m, 2H, CH_2), 1.0 (s, 0.6x(9H), $(CH_3)_3$), and 0.98 (s, 0.4x(9H), $(CH_3)_3$).

[0135] A sample of 2-*tert*-butyl-thiazolidine-4-carboxylic acid (compound 9), was placed in a 7.5 ml vial and sealed with an appropriate stopper. 1.5 ml of rpmi and 0.5 ml of TBHP were added, and the vial was placed at 37°C with orbital stirring. At the appropriate time, 250 µl of the gas mixture was analysed as described for Example 1.

[0136] As shown in Figure 16, 2-*tert*-butyl-thiazolidine-4-carboxylic acid (0.11 M) released CO under these conditions. The CO release was fast within the first 6 hours, reaching values around 16%, and then slowed down, reaching 20% within one day.

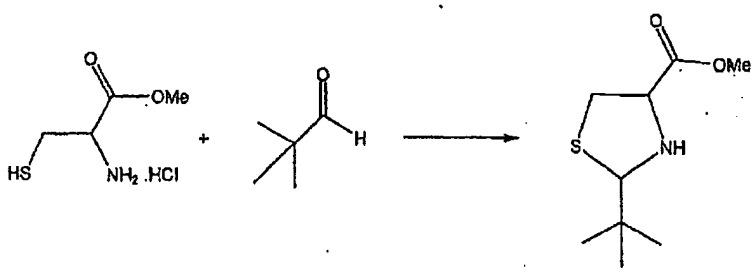
Example 11: Preparation of 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester (compound 10) and CO release from 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester in TBHP

[0137] 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester (compound 10)



(10)

was synthesized and tested for CO release in TBHP. The compound was prepared as illustrated in equation 16:



(16)

Specifically, the preparation of 2(RS)-*tert*-butyl-thiazolidine-4(R)-carboxylic acid methyl ester

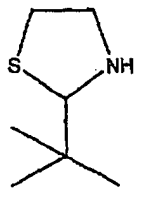
(compound 10) was performed according to the methods described in U.S. Patent No. 6,251,927. L-cysteine methyl ester hydrochloride (1.61 g, 9.2 mmol), trimethylacetaldehyde (1 ml, 1.1 eq) and triethylamine (1 eq., 9.2 mmol, 1.28 ml) were mixed in 20 ml of water. The solution was stirred at room temperature for two days, and a transparent and oily material deposited at the bottom of the flask. Dichloromethane was added and the mixture extracted. The combined organic phases were dried with Na_2SO_4 and the solvent evaporated to yield a transparent oil. Elemental analysis Exp (Calc) C: 52.86 (53.17); H: 7.95 (8.43); N 6.84 (6.89); S 15.43 (15.77); IR ν (cm-1) = 3330, 2967, 2875, 1481, 1366, 1204, 836, 719; ^{1}H-NMR (D_2O) δ: 4.47(s, 0.3H, S-C<u>H</u>-NH), 4.40 (d, J= 3.3 Hz, 0.7H, S-C<u>H</u>-NH), 4.10-4.08 (m, 0.3H, CH_2-C<u>H</u>-NH), 3.80-3.70 (m, 0.6H, CH_2-C<u>H</u>-NH), 3.73 (s, 3H, O<u>C</u>H_3), 3.23-2.24 (m, 2H, CH_2), 1.03 (s, 0.7x(9H), $(CH_3)_3$), and 0.93 (s, 0.3x(9H), $(CH_3)_3$).

[0138] A sample of the 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester (compound 10), was placed in a 7.5 ml vial and sealed with an appropriate stopper, and the CO release experiment was performed as described above in Example 10.

[0139] As shown in Figure 17, 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester (0.1 M) released CO under the test conditions, but the release was very slow, with only 0.3% of CO released after 6 hours. After one day, the maximum CO release was about 10%. These results were likely due to the lower water solubility of compound 10 as compared to compound 9.

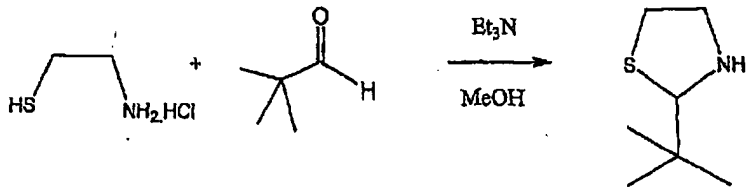
<u>Example 12: Preparation of 2-*tert*-butyl-thiazolidine (compound 11) and CO release from 2-*tert*-butyl-thiazolidine in TBHP</u>

[0140] 2-*tert*-butyl-thiazolidine (compound 11)



(11)

was synthesized and tested for CO release in TBHP. The compound was prepared as illustrated in equation 17:



(17)

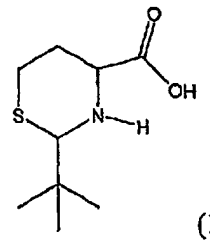
Specifically, the preparation of 2-(RS)-*tert*-butyl-thiazolidine was performed according to a method related to that described by Jellum et al., *Anal. Biochem.* 31:339-347 (1969). Cysteamine hydrochloride (2.01 g, 17.69 mmol) and trimethylacetaldehyde (2.35 ml, 1.2 eq.) were mixed in methanol (20 ml) at room temperature. Triethylamine (2.55 ml, 1.05 eq.) was added, and the mixture was stirred for 2 hours at room temperature. The solvent was then removed under vacuum, yielding a white gummy solid. Diethyl ether and aqueous $NaHCO_3$ saturated were added. The mixture was extracted, and the combined organic phases were dried (Na_2SO_4) and evaporated to yield a transparent oil. IR ν (cm^{-1}) = 3321, 2971, 1673, 1482, 1371, 1050, 927, 839; ^{1}H-NMR (CDCl3) δ: 4.4 (s, 1H, C<u>H</u>), 3.64-3.53 (m, 0.65x2H, NH-C<u>H</u>$_2$), 2.96-2.80 (m, 2H, S-C<u>H</u>$_2$), 2.68-2.60 (m, 0.35x2H, NH-C<u>H</u>$_2$), 1.03 (s, 0.65x9H, $(CH_3)_3$), 1.0 (s, 0.35x9H, $(CH_3)_3$).

[0141] A sample of the 2-*tert*-butyl-thiazolidine (compound 11), was placed in a 7.5 ml vial and sealed with an appropriate stopper, and the CO release experiment was performed as described above in Example 10.

[0142] As shown in Figure 18, 2-*tert*-butyl-thiazolidine (0.14 M) released CO under these conditions, initially very slowly, then reaching high values of about 25% after one day.

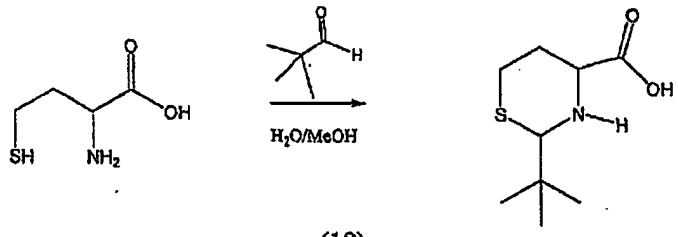
<u>Example 13: Preparation of 2(RS)-*tert*-butyl-[1,3]thiazinane-4(RS)-carboxylic acid (compound 12) and CO release from 2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid in TBHP</u>

[0143] 2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid (compound 12)



(12)

was synthesized and tested for CO release in TBHP. The compound was prepared as illustrated in equation 18:



(18)

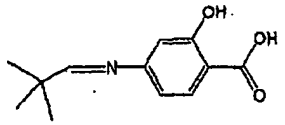
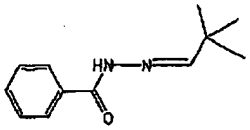
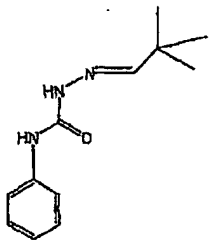
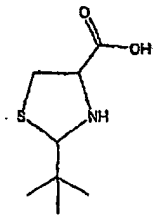
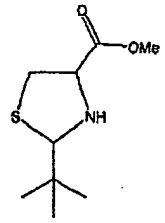
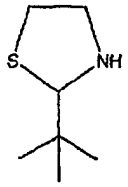
Specifically, the preparation of 2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid was performed according to the procedure used in the preparation of compound 9. DL-Homocysteine (1 g) was dissolved in 10 ml of MeOH and 2 ml of distilled water, and trimethylacetaldehyde (1.2 eq.) was added. The solution was stirred at room temperature for 16 hours, and the solvents evaporated, yielding a white powder. IR ν (cm^{-1}) = 3461, 2936, 2858, 1725, 1455, 1263, 1190, 1023, 908, 828. ^{1}H-NMR (D_2O) δ: 4.28, (s, 0.4x1H, S-C<u>H</u>-NH), 4.17 (s, 0.6x 1H, S-C<u>H</u>-NH), 4.02-4.03 (m, 0.4xH, CH_2-C<u>H</u>-NH), 3.7-3.4 (m, 0.6x1H, CH_2-C<u>H</u>-NH), 2.93-2.55 (m, 2H, S-C<u>H_2</u>), 2.49-1.76 (m, 2H, C<u>H_2</u>-CH-NH), 0.98 (s, 0.4x(9H), $(CH_3)_3$), and 0.96 (s, 0.6x(9H), $(CH_3)_3$).

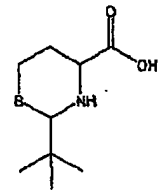
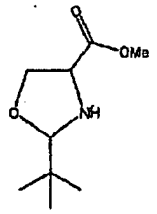
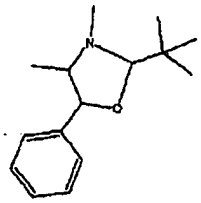
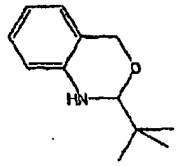
[0144] A sample of 2-tert-butyl-[1,3]thiazinane-4-carboxylic acid (compound 12) at a concentration of 0.1M was placed in a 7.5 ml vial and sealed with an appropriate stopper. The CO release experiment was performed as described above in Example 10.

[0145] As shown in Figure 19, 0.1M 2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid exhibited CO release lower than its 5-membered ring analogue, reaching values of about 16% after one day. Compound 12 has good water solubility, so these results likely are due to reduced ring opening reactivity.

[0146] Table 1 summarizes the results of CO release experiments on various aldehyde prodrug compounds. The experiments were performed as described in Example 10. The results for compounds 9-12, generated as detailed in Examples 10-13, are included.

Table 1

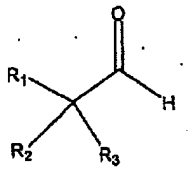
Compound	CO Release
 cis/trans mixture	Stable, but instantaneous hydrolysis was observed when dissolved in water
	No hydrolysis → No CO
	No hydrolysis → No CO
	17% after 5 hours 21% after 23 hours
	0.3% after 6 hours 10.3 % after 25 hours
	3% after 6 hours 25% after 24 hours

	7.7% after 6 hours 15.8% after 25 hours
	0% after 6 hours 4.2% after 24 hours
	No hydrolysis → No CO
	No hydrolysis → No CO

[0147] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only, that the claimed invention may be practiced otherwise than as specifically illustrated, and that many modifications and variations will fall within the spirit and scope of that which is described and claimed.

CLAIMS

1. A method for treating inflammatory disease in an animal in need thereof, comprising administering to the animal a pharmaceutical composition including an anti-inflammatory effective amount of a compound of formula I:



(I)

wherein R_1, R_2 and R_3 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, hydroxy, alkoxy, amino, alkylamino, mercapto, alkylmercapto, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, alkoxycarbonyl, acyl, acyloxy, acylamino, alkylsulfonyl, alkylsulfinyl, F, Cl, Br, NO_2 and cyano; or two or more of R_1, R_2 and R_3 are taken together to form a substituted or unsubstituted carbocyclic or heterocyclic ring structure,

or a derivative thereof, in a pharmaceutically acceptable vehicle.

2. The method of claim 1, wherein R_1, R_2 and R_3 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, and substituted alkenyl.

3. The method of claim 2, wherein the compound of formula I is trimethylacetaldehyde, 2,2-dimethyl-4-pentenal, 4-ethyl-4-formyl-hexanenitrile, 3-hydroxy-2,2-dimethylpropanal, 2-formyl-2-methyl-propylmethanoate or 2-ethyl-2-methyl-propionaldehyde.

4. The method of claim 1, wherein R_1 and R_2 are each independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, and substituted alkenyl, and R_3 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and substituted alkylaryl.

5. The method of claim 4, wherein the compound of formula I is 2,2-dimethyl-3-(*p*-methylphenyl)propanal or 2-methyl-2-phenylpropionaldehyde.

6. The method of claim 1, wherein the derivative of a compound of formula I is an acetal, hemiacetal, aminocarbinol, aminal, imine, enaminone, imidate, amidine, iminium salt, sodium bissulfite adduct, hemimercaptal, dithioacetal, 1,3-dioxepane, 1,3-dioxane, 1,3-dioxalane, 1,3-dioxetane, α-hydroxy-1,3-dioxepane, α-hydroxy-1,3-dioxane, α-hydroxy-1,3-dioxalane, α-keto-1,3-dioxepane, α-keto-1,3-dioxane, α-keto-1,3-dioxalane, α-keto-1,3-dioxetane, macrocyclic ester/imine, macrocyclic ester/hemiacetal, oxazolidine, tetrahydro-1,3-oxazine, oxazolidinone, tetrahydro-oxazinone, 1,3,4-oxadiazine, thiazolidine, tetrahydro-1,3-thiazine, thiazolidinone, tetrahydro-1,3-thiazinone, imidazolidine, hexahydro-1,3-pyrimidine, imidazolidinone, tetrahydro-1,3-pyrimidinone, oxime, hydrazone, carbazone, thiocarbazone, semicarbazone, semithiocarbazone, acyloxyalkyl ester derivative, O-acyloxyalkyl derivative, N-acyloxyalkyl derivative, N-Mannich base derivative or N-hydroxymethyl derivative.

7. The method of claim 6, wherein the derivative is an oxazolidine, thiazolidine, imidazolidinone or oxazolidinone.

8. The method of claim 1, wherein the compound of formula I is linked to an amino acid or protein.

9. The method of claim 1, wherein the compound of formula I or derivative thereof is administered concomitantly with a second anti-inflammatory agent.

10. The method of claim 1, wherein the pharmaceutical composition is a tablet, dragee, capsule, pill, powder, troche or granule.

11. The method of claim 1, wherein the pharmaceutical composition is a suspension, emulsion, solution, syrup or elixir.

12. The method of claim 1, wherein the pharmaceutical composition is formulated for parenteral administration.

13. The method of claim 1, wherein the inflammatory disease is arthritis.

14. The method of claim 13, wherein the inflammatory disease is rheumatoid arthritis.

15. The method of claim 13, wherein the inflammatory disease is juvenile idiopathic arthritis, osteoarthritis or psoriatic arthritis.

16. The method of claim 1, wherein the inflammatory disease is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis or multiple sclerosis.

17. The method of claim 1, wherein the inflammatory disease is an inflammatory lung disease.

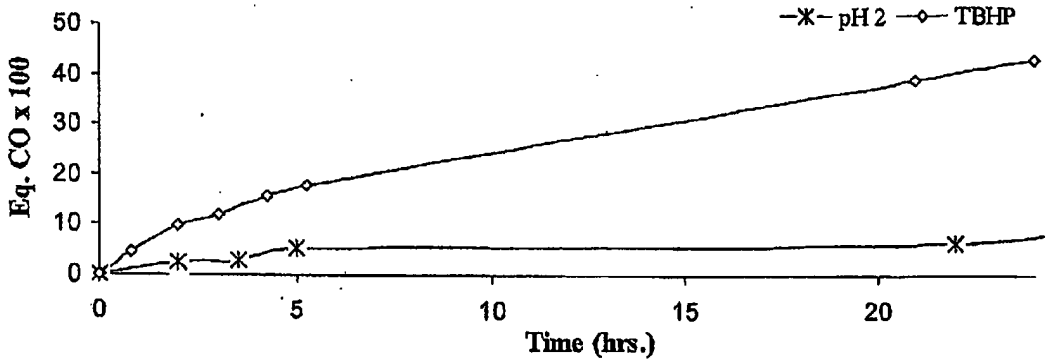
18. The method of claim 1, wherein the inflammatory disease is an inflammatory bowel disease.

19. The method of claim 1, wherein the inflammatory disease is an inflammatory skin disease.

20. The method of claim 1, wherein the inflammatory disease is atherosclerosis, myocardial infarction, stroke or transplant rejection.

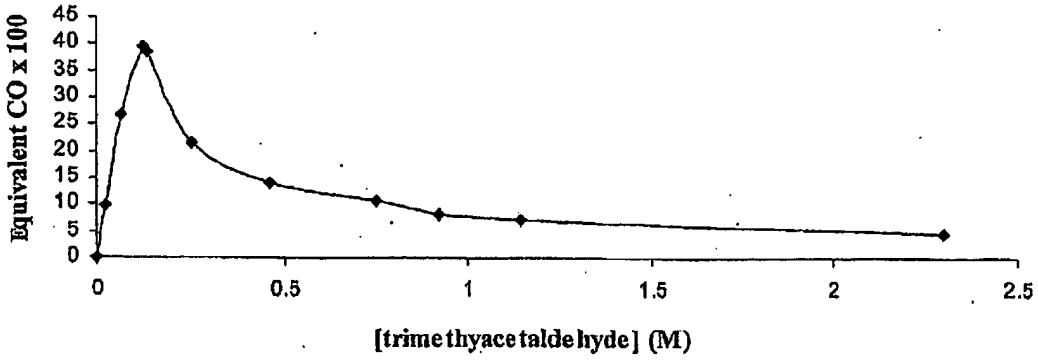
21. The method of claim 1, wherein the inflammatory disease is gram-positive or gram negative shock, sepsis, septic shock, hemorrhagic or anaphylactic shock, or systemic inflammatory response syndrome.

Fig. 1A CO release by Trimethylacetaldehyde (compound 1)



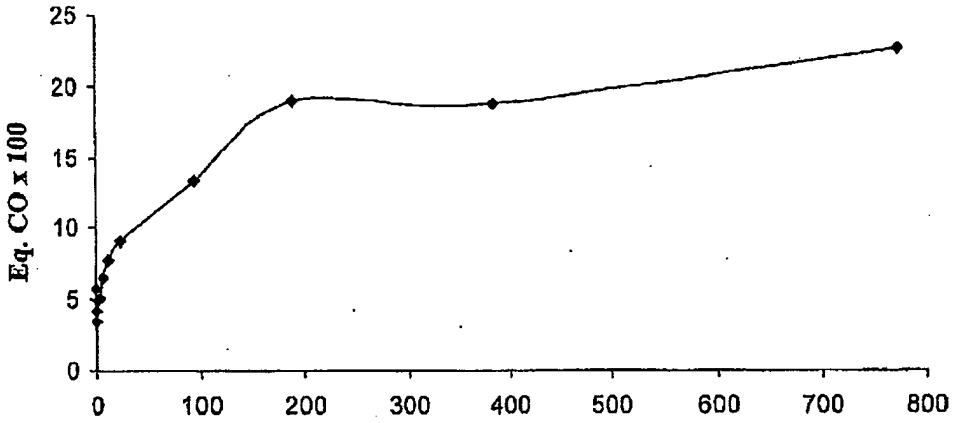
[Trimethylacetaldehyde] = 0.11 M

Fig. 1B



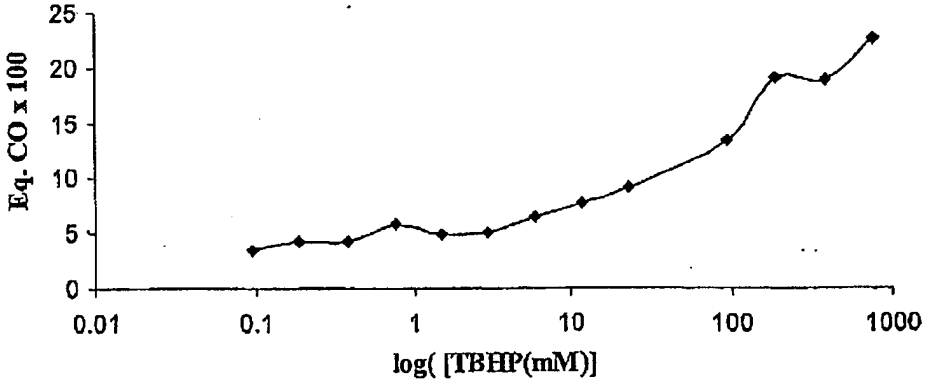
[TBHP] = 1.9M

Fig. 1C CO release by Trimethylacetaldehyde (compound 1) in different TBHP concentrations



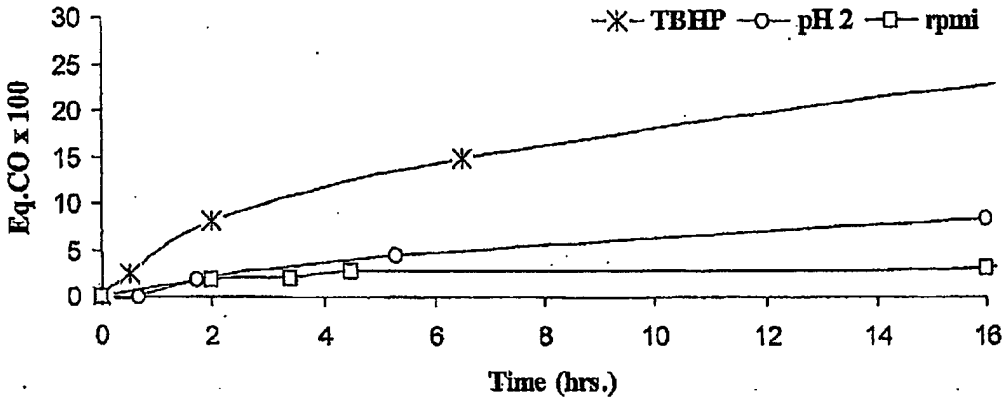
[Trimethylacetaldehyde] = 0.23 M

Fig. 1D



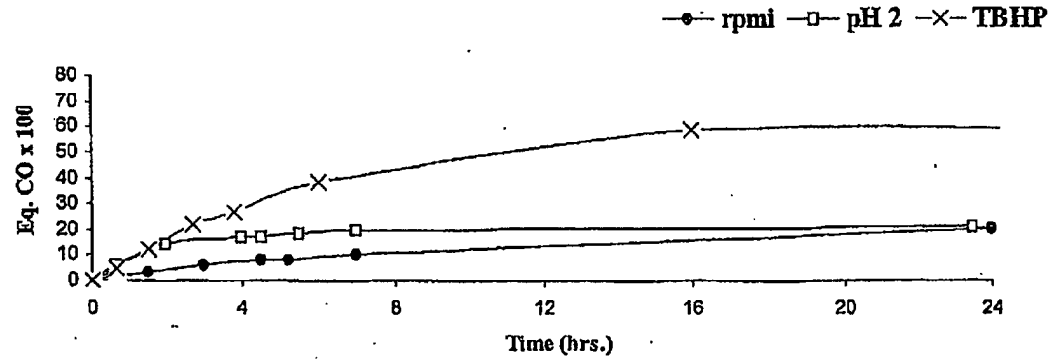
[Trimethylacetaldehyde] = 0.23 M

Fig. 2 CO release by 2,2-Dimethyl-4-pentenal (Compound 2)



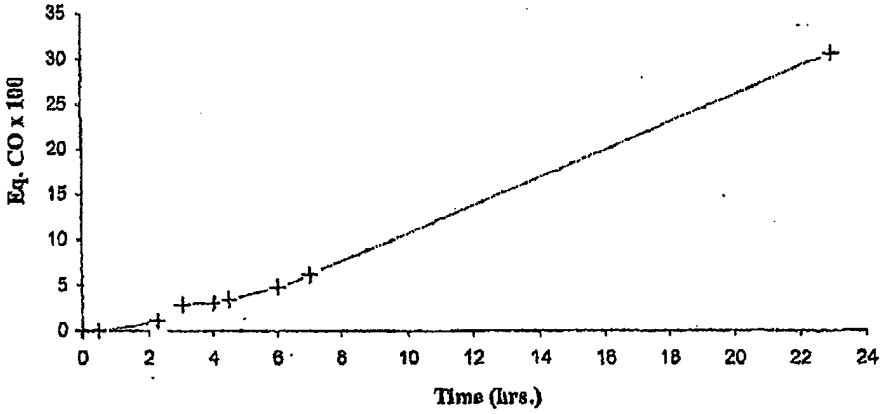
2,2-dimethyl-4-pentenal (C = 0.16 M)

Fig. 3 CO release by 4-ethyl-4-formyl-hexenenitrile (Compound 3)



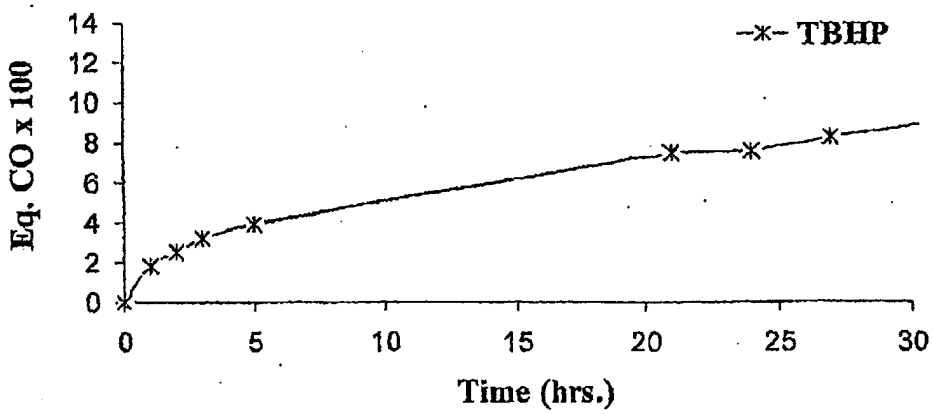
[4-ethyl-4-formyl-hexanenitrile] = 0.15 M

Fig. 4 CO release by 3-hydroxy-2,2-dimethylpropanal (Compound 4)



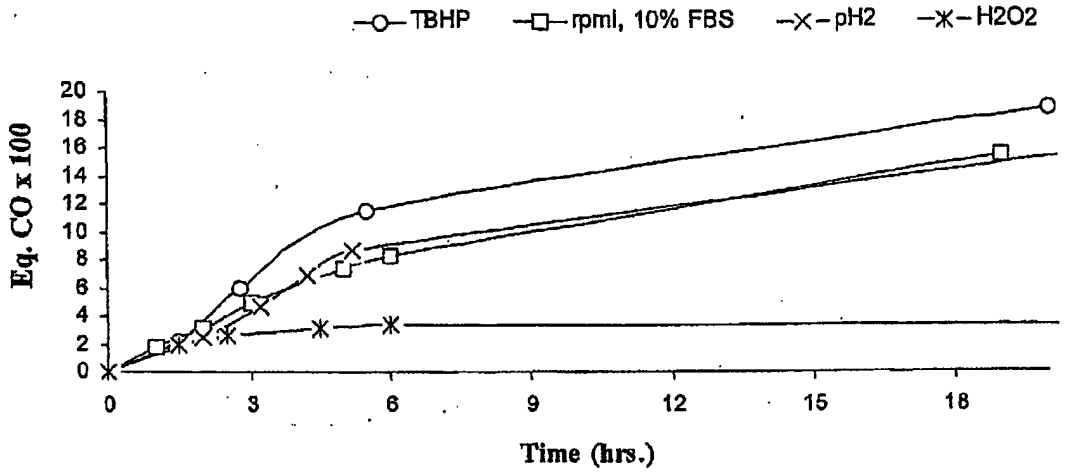
[3-hydroxy-2,2-dimethylpropanal] = 0.12M

Fig. 5 CO release by 2-formyl-2-methylpropylmethanoate (Compound 5)



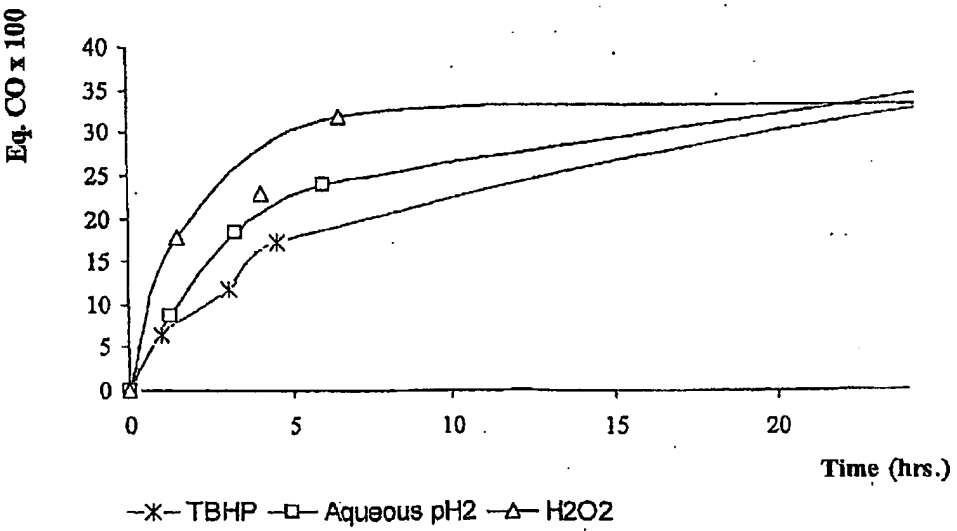
[2-formyl-2-methyl-propylmethanoate] = 0.17M

Fig. 6 CO release by 2,2-dimethyl-3-(*p*-methylphenyl)propanal (Compound 6)



[2,2-dimethyl-3-(p-methylphenyl)propanal] = 0.14M

Fig. 7 CO release by 2-Methyl-2-phenyl-propionaldehyde (Compound 7)



[2-Methyl-2-phenylpropionaldehyde] = 0.16 M

Fig. 8 Kinetics of CO release for compounds 1-7 in the first 6 hours in TBHP solutions

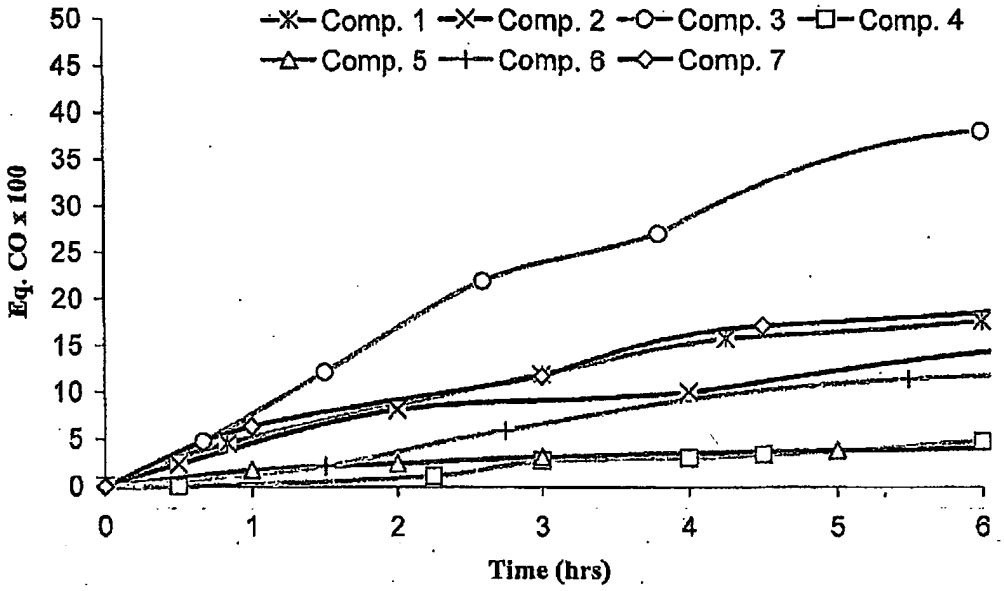


Fig. 9 Kinetics of CO release for compounds 1-7 after 24 hours in different media

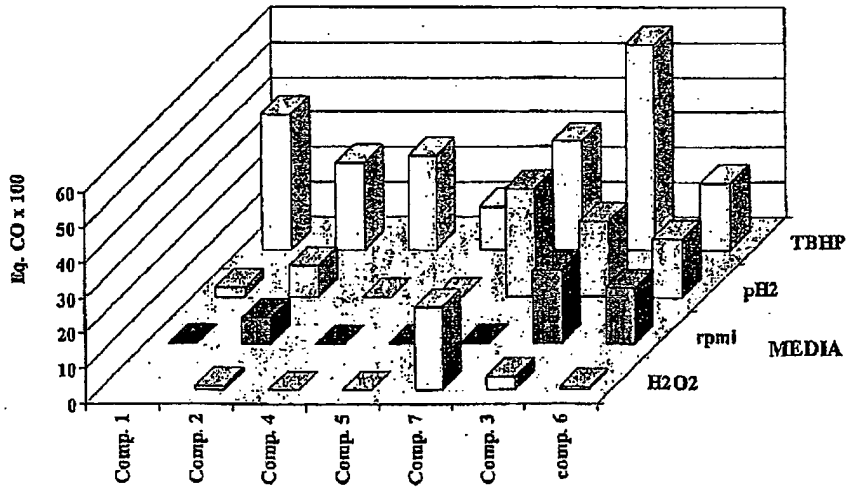


Fig. 10 Changes of body weight in untreated and treated Sprague Dawley rats after induction of adjuvant arthritis

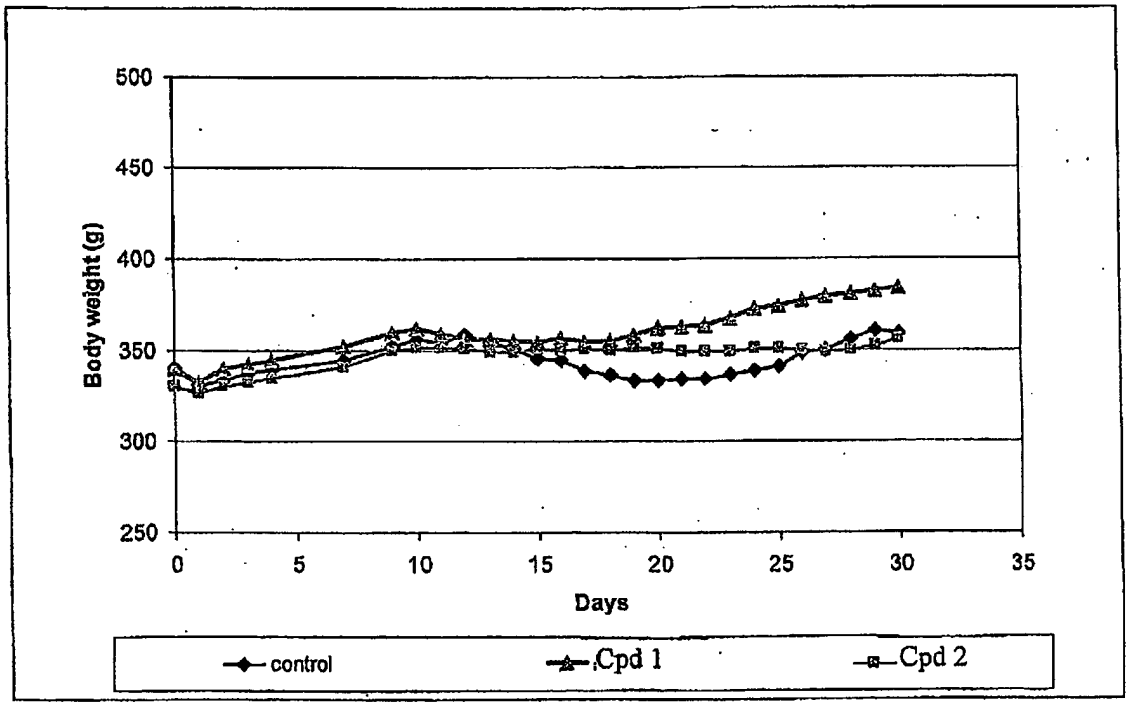


Fig. 11A Changes of right paw volume in untreated and treated Sprague Dawley rats after induction of adjuvant arthritis

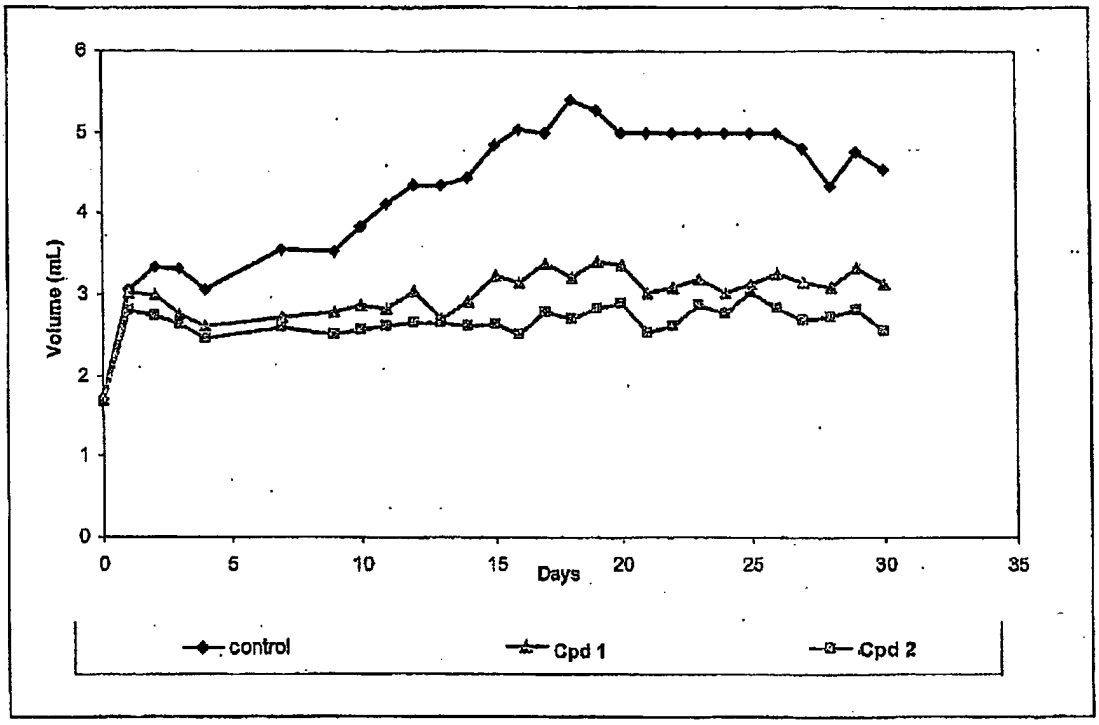


Fig. 11B Changes of left paw volume in untreated and treated Sprague Dawley rats after the induction of adjuvant arthritis

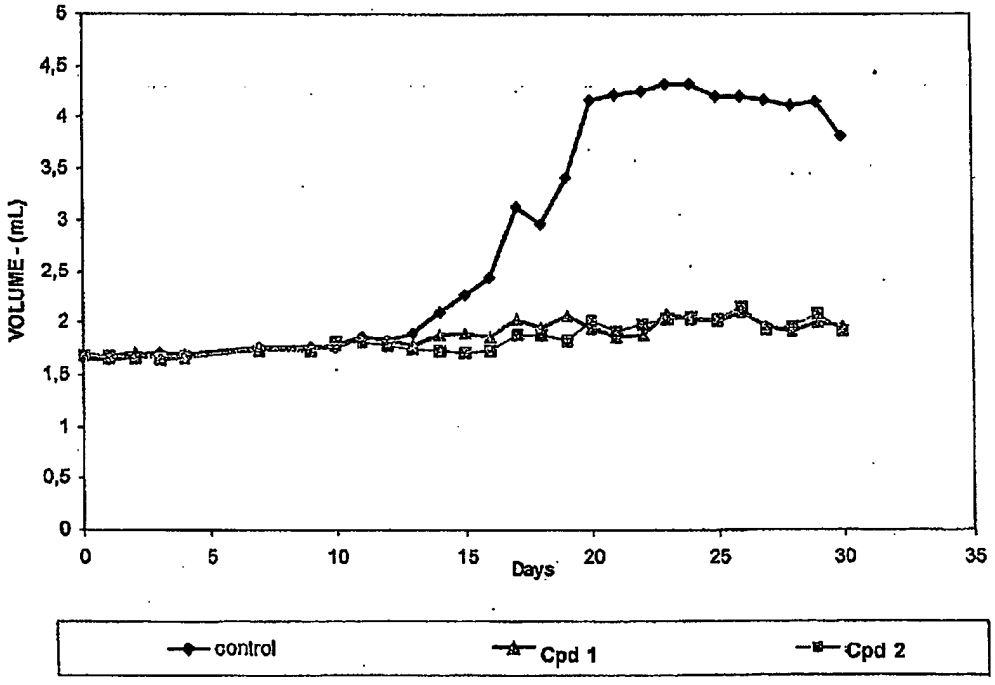


Fig. 11C Changes of right paw circumference in untreated and treated Sprague Dawley rats after induction of adjuvant arthritis

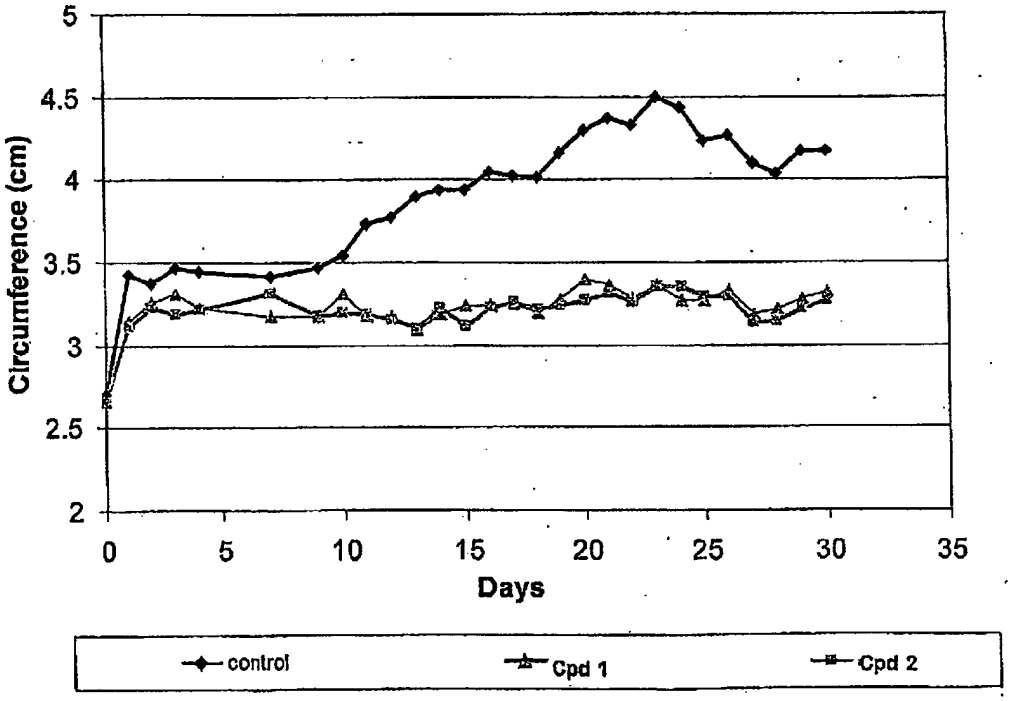


Fig. 11D Changes of left paw circumference in untreated and treated Sprague Dawley rats after induction of adjuvant arthritis

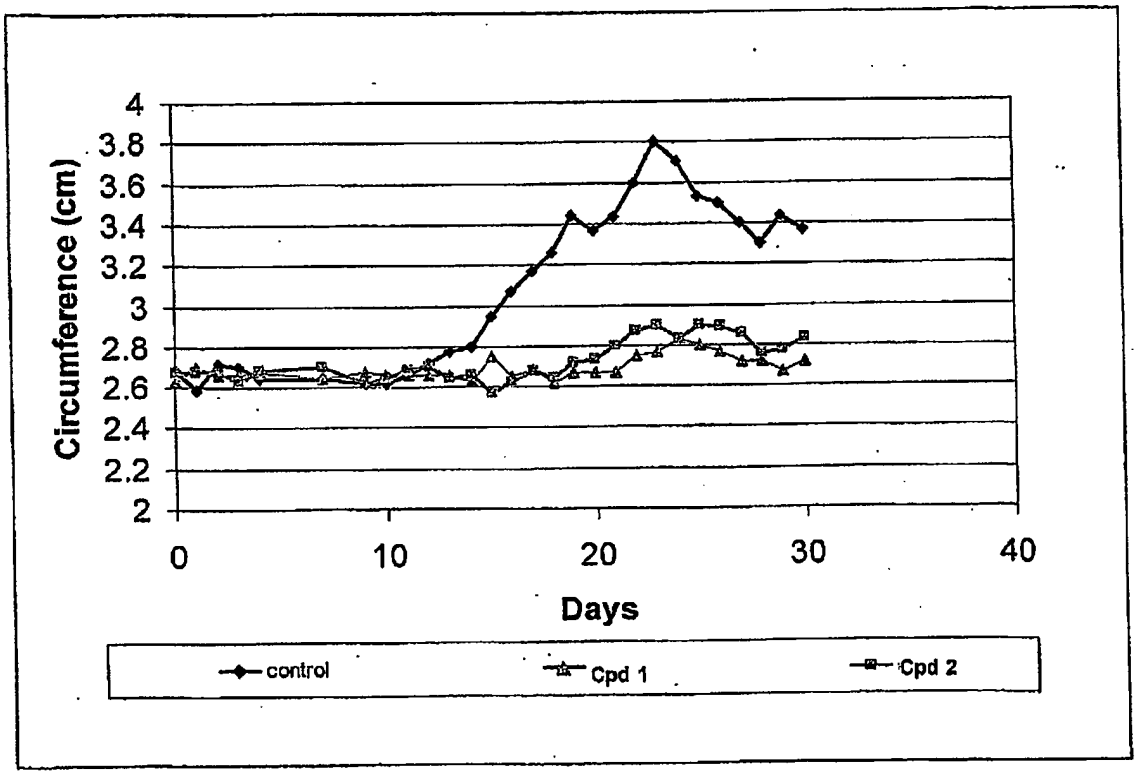


Fig. 12 Changes of arthritic index in untreated and treated Sprague Dawley rats with adjuvant arthritis

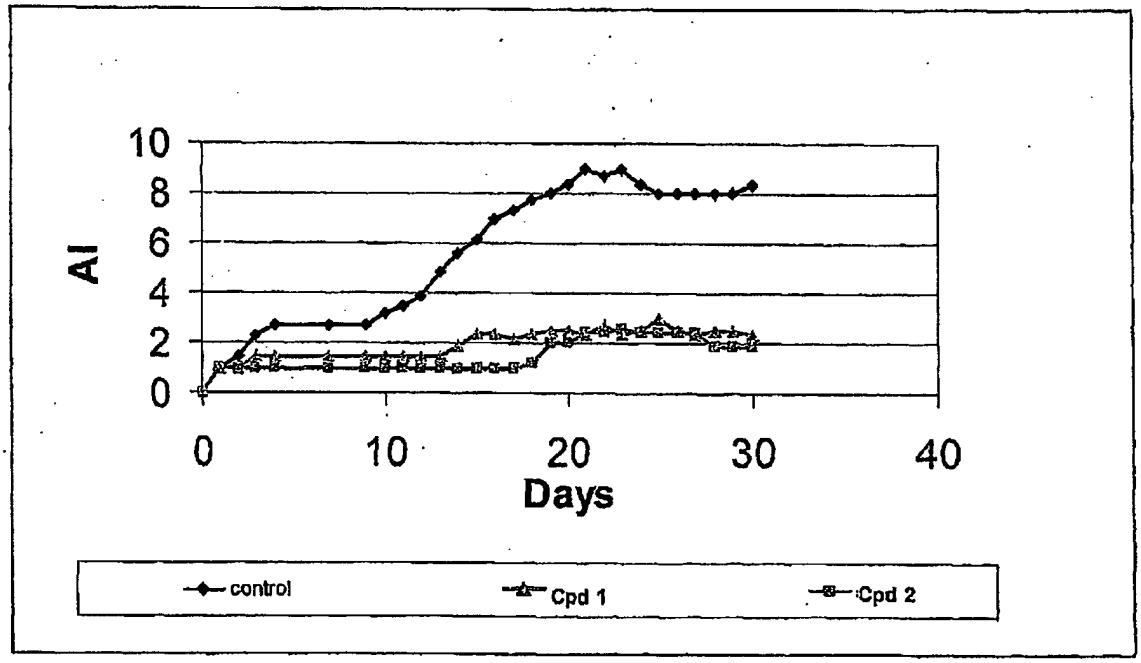


Fig 13 Changes of body weight in untreated and treated Lewis rats with adjuvant arthritis

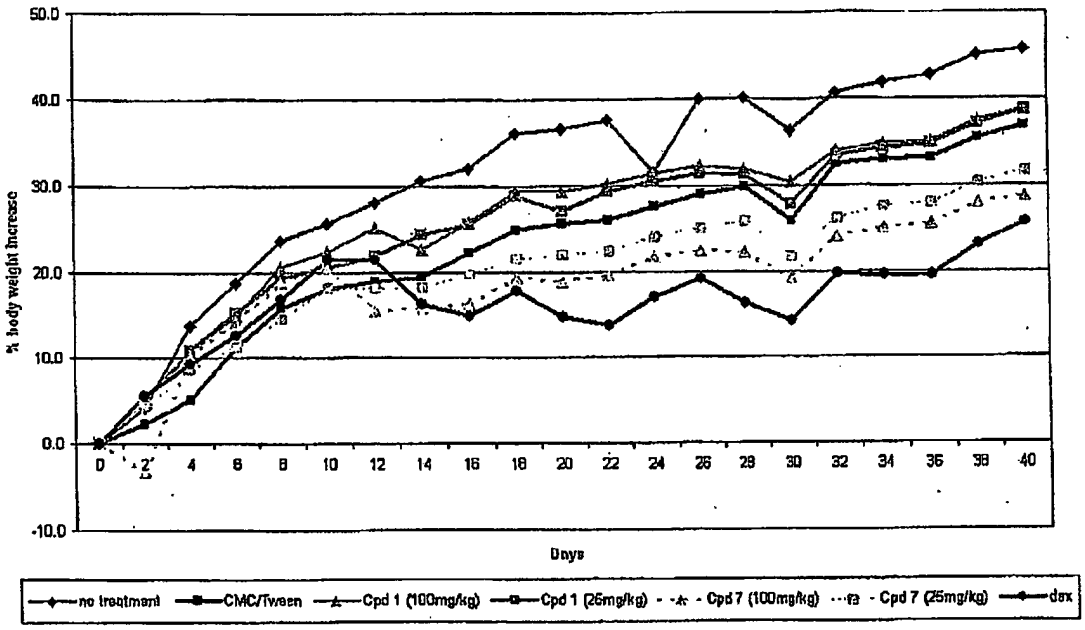


Fig. 14 Changes in paw volume in untreated and treated Lewis rats with adjuvant arthritis

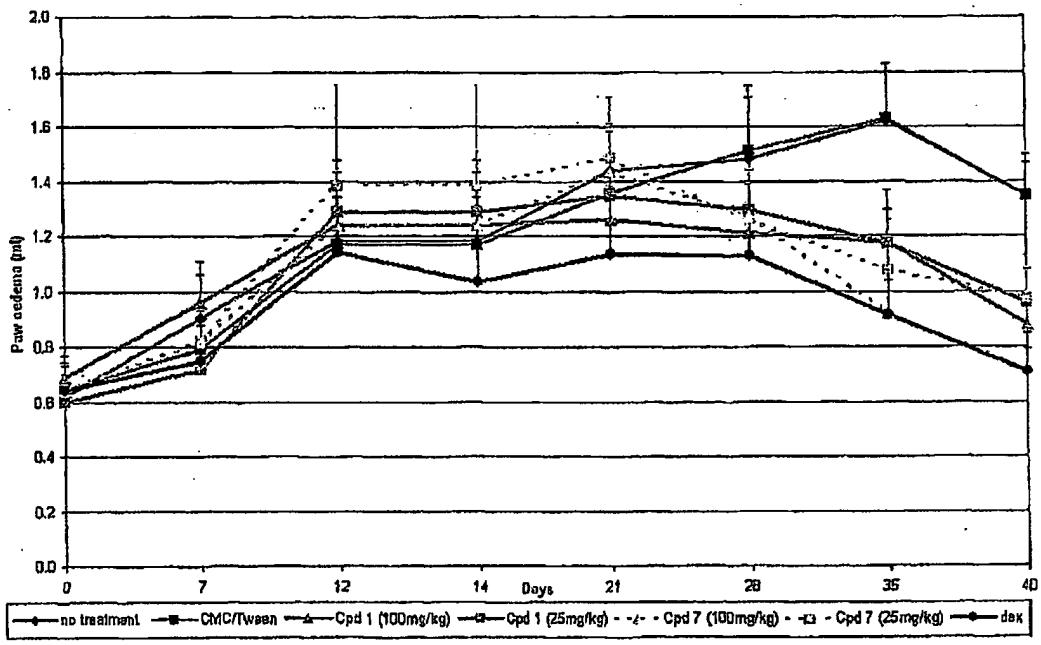


Fig. 15 Changes in arthritic index in untreated and treated Lewis rats with adjuvant arthritis

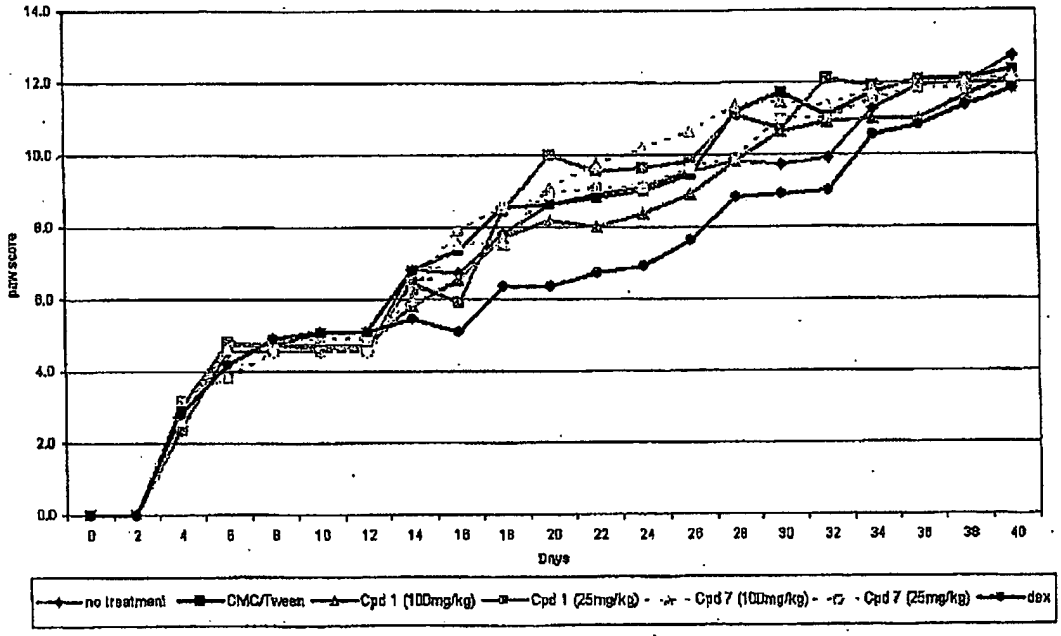
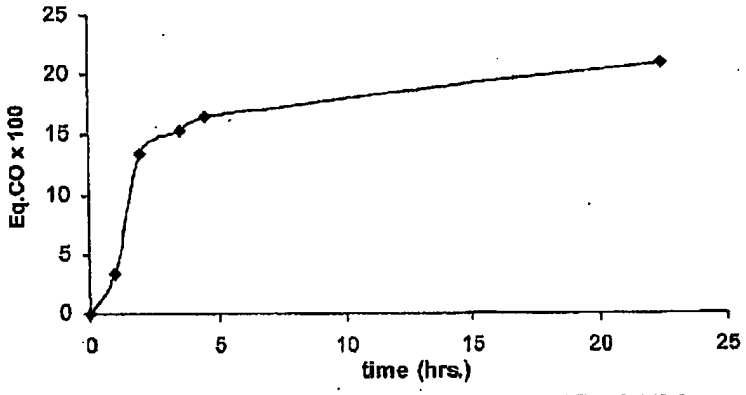
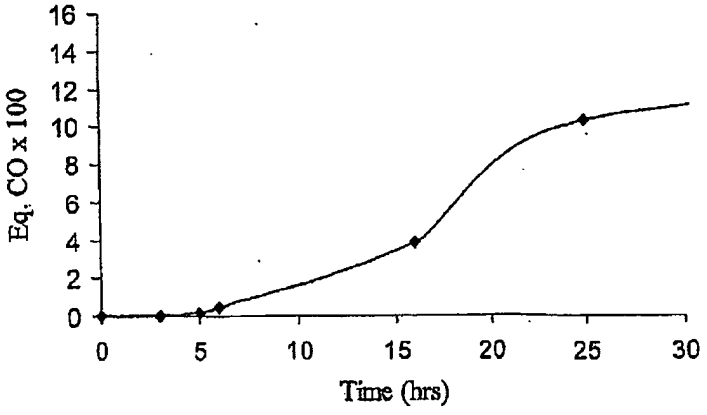


Fig. 16 CO release by 2-*tert*-butyl-thiazolidine-4-carboxylic acid (Compound 9)



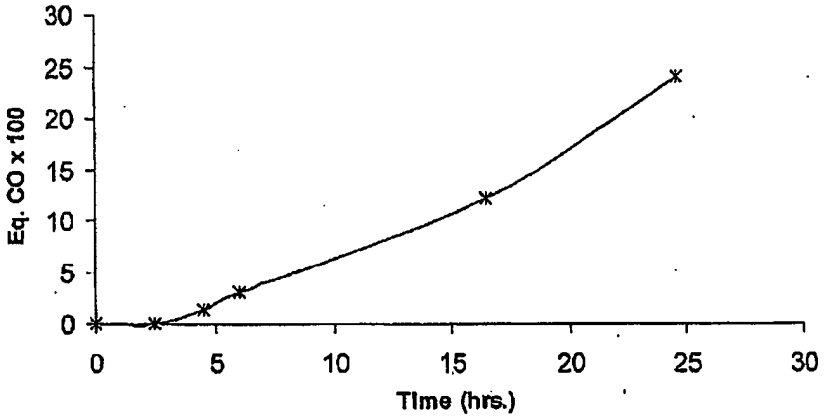
[2-*tert*-butyl-thiazolidine-4-carboxilic acid] = 0.11M

Fig. 17 CO release by 2-*tert*-butyl-thiazolidine-4-carboxylic acid methyl ester (Compound 10)



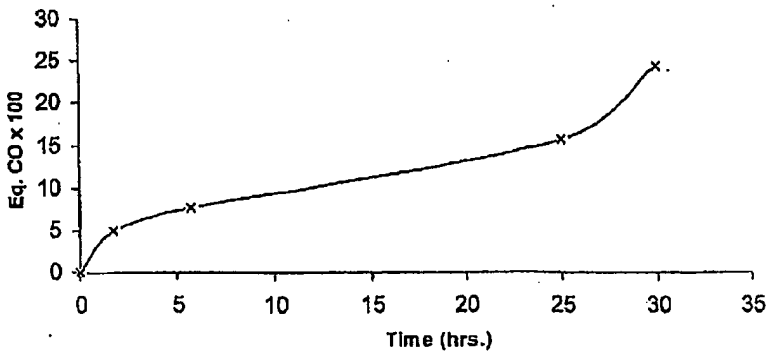
[2-*tert*-butyl-thiazolidine-4-carboxilic acid methyl ester] = 0.1M

Fig. 18 CO release by 2-*tert*-butyl-thiazolidine (Compound 11)



[2-*tert* -butyl-thiazolidine] = 0.14 M

Fig. 19 CO release by 2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid (Compound 12)



[2-*tert*-butyl-[1,3]thiazinane-4-carboxylic acid] = 0.1M

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(57) Abstract: A method is disclosed for treating inflammatory disease in an animal in need thereof by administering to the animal a pharmaceutical composition containing an anti-inflammatory effective amount of an organic aldehyde compound or a derivative thereof in a pharmaceutically acceptable vehicle.

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